Coordinated Management of Young-Onset Parkinson’s Disease

Although Parkinson’s disease typically affects people over the age of 65, the condition can develop years earlier. Mayo Clinic is launching a young-onset Parkinson’s disease clinic to meet the distinct needs of people who have a diagnosis of this neurodegenerative condition (Figure 1) at a younger age.

“The implications are very different for patients in the prime of life who are still working, perhaps raising children and have an active lifestyle,” says Rodolfo Savica, M.D., Ph.D., a neurologist at Mayo Clinic in Rochester, Minnesota. “There is an entire spectrum of limitations that these patients must deal with, beyond tremor, rigidity or stiffness. It can be devastating.”

Sleep disturbances, anxiety and depression are common (Figure 2). “These problems frequently occur prior to the movement troubles that help cinch the diagnosis of Parkinson’s disease. They’re also often far more disabling in young-onset Parkinson’s than are the motor troubles experienced early in the course of the disease,” says Ryan J. Uitti, M.D., a neurologist at Mayo Clinic in Jacksonville, Florida. “We should always address quality of life for people with Parkinson’s disease, but that’s particularly important for younger patients.”

Efficient multidisciplinary care

As a tertiary center, Mayo Clinic has experience with the diagnosis and treatment of uncommon conditions such as young-onset Parkinson’s disease. No specific age cutoff defines young onset, but most patients are in their 50s.

“A younger patient might not have the classic tremor, but might instead present with a lower extremity dystonia or perhaps upper extremity stiffness or rigidity,” says Shyamal H. Mehta, M.D., Ph.D., a neurologist at Mayo Clinic in Phoenix/Scottsdale, Arizona. “The diagnosis can be delayed in these younger patients because the possibility of Parkinson’s disease might not be considered.”

At Mayo, the young-onset Parkinson’s disease clinic is designed to provide multidisciplinary evaluation and management in a single two-day visit. Laboratory testing is performed, as well as neuroimaging when needed. Mayo Clinic uses state-of-the-art diagnostic tools, including electrophysiological testing, functional imaging and radionuclide injections (Figure 3). Radionuclide testing is often recommended in younger patients to support a clinical diagnosis of Parkinson’s disease.
Patients then typically see specialists in:

- Movement disorders
- Sports medicine, who can provide advice geared to individuals’ favored exercise, such as cycling or swimming
- Sleep medicine
- Genetics, who can advise on genetic variations that might increase the risk of Parkinson’s disease for family members
- Integrative medicine

Before patients arrive at Mayo Clinic, they complete intake questionnaires about their problems and concerns. “This allows us to set up additional specialist appointments as needed — for example, in urology, psychiatry, and men’s or women’s health,” Dr. Savica says. “The entire set of specialists is ready for the patient when he or she arrives.”

During their visits, patients might be offered opportunities to participate in research. Before leaving Mayo, patients receive a summary of the information provided to them. Full reports are also sent to patients’ local clinicians.

To minimize the need for in-person follow-up, Mayo Clinic is developing methods for ongoing contact via personal electronic media. “Staying in close contact electronically with patients and their local clinicians allows us to suggest changes in therapy that can improve quality of life, without patients’ having to make three or four visits to Mayo a year. This is very important for people who are working and have families,” Dr. Uitti says.

**Individualized treatment and therapeutic trials**

Therapy for young-onset Parkinson’s disease depends on a patient’s needs and level of impairment. “Our recommendations are guided by the differing disease course we typically see in young-onset Parkinson’s disease,” Dr. Savica says. “Young-onset patients usually, but not always, have more dyskinesias. However, because of the rarity of young-onset Parkinson’s disease, there is much about the disease course that is still unclear.”

In addition to medication, deep brain stimulation (DBS) is a treatment option at all three Mayo Clinic campuses. “If we are unable to ameliorate a patient’s symptoms adequately with medication, we may put in as many as four brain electrodes (Figure 4) rather than the standard two. We have found that this can significantly improve patients’ quality of life,” Dr. Uitti says. “Our preferred DBS system has

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**Figure 2.** Chart illustrates the timeline of events, signs and symptoms that precede Parkinson’s disease.

**Figure 3.** After injection of the radioligand ioflupane (DaTscan), single-photon emission computerized tomography (SPECT) brain imaging provides visualization of the striatal dopamine transporter. This technique is of diagnostic value in patients with young-onset Parkinson’s disease, who may present with atypical signs and symptoms.

**Figure 4.** Image shows the placement of bipallidal and bithalamic deep brain stimulation electrodes for treatment of Parkinson’s disease.
eight electrodes that can be used individually or in combination with one another, which gives us a lot of flexibility to influence the brain.”

As a leader in Parkinson’s disease research, Mayo Clinic provides opportunities for patients to participate in therapeutic trials of new medications and surgical techniques. Mayo also offers genetic testing and biobanking of DNA for people with Parkinson’s disease so they can be notified of any future treatments that might benefit them. Among the approximately 20 genes associated with Parkinson’s disease, Mayo Clinic discovered three, including the most common, LRRK2.

Endoscopic Skull Base Surgery: The Advantages of Mayo’s Team Approach

As a fully integrated tertiary medical center, Mayo Clinic provides a comprehensive team approach to endoscopic skull base surgery. At all three Mayo Clinic campuses, neurosurgeons, neurologists, endocrinologists, otolaryngologists and neuro-ophthalmologists collaborate at each step, from preoperative workup through surgery and postoperative care.

“The Mayo Clinic Model of Care is ideal for endoscopic skull base surgery. Patients are best served when they see all of these specialists throughout the process,” says Bernard R. Bendok, M.D., chair of Neurosurgery at Mayo Clinic in Phoenix/Scottsdale, Arizona. “This is where team medicine shines.”

Mayo Clinic specialists have extensive experience with endoscopic skull base surgery for the treatment of pituitary tumors, meningiomas, clival tumors, chordomas and cranioopharyngiomas. Occasionally, the procedure is used to treat certain cavernomas and aneurysms.

Endoscopic skull base surgery can also be combined with proton beam therapy, an approach that can be particularly helpful for the treatment of chordomas. For most patients with pituitary tumors and chordomas, Mayo strives to optimize resection before beginning radiation therapy if that therapy is needed.

“That’s a very important point that isn’t always considered,” Dr. Bendok says. “Skull base tumors can be located near critical radiation-sensitive structures, including the optic nerves (Figure). When a tumor cannot be removed completely, creating space between the residual tumor and the optic nerves can be a worthwhile surgical goal to reduce potential injury to vision. To obtain the optimal surgery, patients should ask how close their tumors are to the optic chiasm and how the surgical team will manage that.”

Maximizing safety during surgery

Mayo Clinic uses sophisticated imaging to enhance the safety of endoscopic skull base surgery, including holography and augmented reality. Both techniques are used preoperatively to visualize and plan the procedure; holography is also used for intraoperative visualization.

“Our visualization in health care to date has been two-dimensional,” Dr. Bendok says. “But holography takes 3D to the next level. It allows everyone in the operating room to understand what’s happening. The enhanced visualization helps the surgeon to perform an optimal surgery.”

Intraoperative CT, MRI and angiography are also key to enhancing safety while providing optimal resection. Mayo Clinic will soon have a hybrid system for intraoperative neurological CT and MRI.

“This is a highly sophisticated operating room with a robotic C-arm that allows us to perform intraoperative CT and then slide the patient over and do intraoperative MRI right next door. It’s very unique,” Dr. Bendok says. “Having CT and MRI, as well as intraoperative angiography, allows us to assess our skull base work with intraoperative and robotic fluoroscopy and to get quick control of the carotid arteries and other vessels if necessary during surgery.”

To reduce the risk of stroke, Mayo Clinic uses balloon test occlusion for high-risk patients, such as those who have had prior radiation or previous surgery. Through the use of nasoseptal or other ancillary flaps for skull base repair, Mayo Clinic has achieved negligible rates of postoperative cerebrospinal fluid leak.
For postoperative care, Mayo Clinic has a neuroscience intensive care unit (ICU) if needed — although most patients can move to a surgical-ward room after endoscopic skull base surgery. “As the surgery has become less invasive, we’ve been able to move away from using the ICU for most of these patients,” Dr. Bendok says.

The team approach continues outside the operating room. Endocrinologists evaluate patients postoperatively in the hospital and again at visits within two weeks of surgery. “If the patient has a local endocrinologist, there is a handoff, with the Mayo skull base team sending a full report,” Dr. Bendok says.

“The pillars that support our skull base surgery practice are the various specialties that work synergistically with our neurosurgeons,” he adds. “Our commitment to that very close integration is the strength we offer to patients.”

Melding Technology and Expertise for Optimal Spinal Surgery

Spinal surgery at Mayo Clinic combines advanced technology with the personalized expertise of a multidisciplinary treatment team. Consultations and surgery are available at all three Mayo Clinic campuses for people with the gamut of spinal conditions, including focal degenerative disease, larger spinal deformity such as scoliosis, and primary and metastatic tumors of the spine. Mayo Clinic’s neurosurgeons work closely with physiatrists to evaluate patients, including people referred for possible revision surgery. “We have a weekly spine conference where we obtain input on patient management from our specialists in physical medicine and rehabilitation, pain medicine and neuroradiology, as well as neurosurgery.
Together, we’re able to address spinal conditions in a variety of ways, to optimize outcomes for our patients,” says Selby G. Chen, M.D., a neurosurgeon at Mayo Clinic in Jacksonville, Florida.

Neuroradiologists at Mayo Clinic have extensive experience reviewing spinal imaging, including CT myelograms and single photon-emission computerized tomography scans. “That advanced imaging is very helpful for us to identify where a patient’s problem and pain originate and to recommend treatment,” Dr. Chen says.

Because Mayo Clinic is a fully integrated practice, treatment decisions are based on patients’ individual needs. “Many patients don’t necessarily need spinal surgery, or may not be good surgical candidates,” Dr. Chen says. “If that’s the case, our physical medicine and rehabilitation specialists are able to take the helm and provide the kind of care these patients need, such as physical therapy, injections or spinal cord stimulation. We can always offer an opinion and suggest a treatment option, either surgical or nonsurgical, even for patients who come to us needing revision after previous surgeries.”

**Latest OR technology**
Mayo Clinic has a new robotic system for spinal surgery that allows for preoperative and intraoperative planning, as well as robotic-guided surgical execution in multiple trajectories. The system’s robotic arm connects directly to the patient’s anatomy during surgery to enhance stability and precision.

In addition, Mayo Clinic uses intraoperative CT with spinal navigation. “That’s especially helpful in revision cases, where the spinal anatomy may not be completely normal,” Dr. Chen says. “We also have a full range of neuromonitoring during surgery, supported by our neuroanesthesiologists.”

These technologies facilitate the use of minimally invasive spinal surgery when appropriate. “Misalignment of the spine at one or two levels; spinal stenosis or instability at a few levels; and herniated disks can definitely be treated through a minimally invasive approach. It is a great option that we can provide for patients,” Dr. Chen says. Minimally invasive spinal surgery uses smaller incisions and generally requires less disruption of soft tissue around the spine, less blood loss and pain, lower rates of infection, and faster recovery.

“The multidisciplinary aspect of our spine care is really unique and definitely helps us improve outcomes,” Dr. Chen says. “That, plus our state-of-the-art technology, means we have a lot of options to offer patients.”

**Investigating Autoinflammatory Epileptic Encephalopathies in Children**

Charles L. Howe, Ph.D., director of the Translational Neuroimmunology Laboratory at Mayo Clinic in Rochester, Minnesota, and Eric T. Payne, M.D., M.P.H., a pediatric epileptologist at Mayo’s campus in Minnesota, answer questions about pediatric epileptic encephalopathies caused by neuroinflammation in the absence of antibodies. These autoinflammatory epilepsies can present with signs and symptoms similar to those of autoimmune epilepsy.

**Q: How is autoinflammatory disease diagnosed?**
Mayo’s Translational Neuroimmunology Laboratory can perform *ex vivo* testing of patients’ blood samples to measure levels of cytokines associated with autoinflammatory disease, such as IL-1 beta, TNF and IL-6. We are working to develop higher throughput testing panels similar to those that Mayo offers for autoimmune neurology.

**Q: What should physicians look for when considering autoinflammatory disease testing?**
Our investigations into these conditions are just starting, so it’s going to be a moving target. But often these children are previously well and cognitively normal, and present with an explosive onset of seizures that don’t respond to anti-seizure medications. Investigative tests and standard neuroimaging fail to identify an underlying cause or detect the neuroinflammation that is continuing to drive seizures and affect cognition.

Autoinflammation has been identified in children with febrile infection-related epilepsy...
syndrome (FIRES), a devastating epileptic encephalopathy that requires a prior febrile infection occurring between two weeks and 24 hours before the onset of refractory status epilepticus — with or without fever at the onset of seizures. A child might get a cold and a bit of a fever, and then a day or two later, the unrelenting seizures start.

Autoinflammation has also been identified in kids with electrographic status epilepticus in sleep, in children with febrile status epilepticus who later developed mesial temporal sclerosis and even in a teenager with presumed new-onset juvenile myoclonic epilepsy — a relatively common generalized epilepsy.

Q: How are autoinflammatory-mediated seizure disorders treated?
Typically, a steroid — such as methylprednisolone, which blocks inflammation broadly — is trialed first. Sometimes patients may respond to this temporarily, and other times it does not work at all. But if we can identify a specific inflammatory target that is driving the inflammatory process, we can use more-precise immunomodulatory treatments to block that specific cytokine pathway. Many of these precision immunomodulatory treatments have already been approved by the Food and Drug Administration for use in children and have good longitudinal safety profiles. Our rheumatology colleagues have treated patients with these medications regularly for many years.

A few years ago, Mayo Clinic was the first to successfully treat a 2-year-old girl with FIRES using anakinra, a drug that blocks the effects of IL-1 beta. Since then, we have learned that although anakinra isn’t always effective in children with FIRES, a substantial number do indeed respond robustly. FIRES is a multifactorial condition that likely varies with a child’s genetics, and the cause isn’t fully elucidated. But autoinflammation seems to play a key role in the disease pathology for some patients.

We do know that, in general, the earlier we can intervene, the sooner the seizure resolution and the outcome. Our index patient has evidence on imaging of some damage to the brain, and we started treating her six days after seizure onset. But we also have examples of patients who began treatment 30 days after seizure onset and still benefit from therapy. A one- or two-week trial should be sufficient to know if the therapy is helping; sometimes the benefits are apparent within a few days.

We have seen enough of these patients to know how the condition is likely to progress. It’s important to understand that the potential benefits of starting treatment far outweigh any risk.

Q: What has Mayo Clinic learned about biomarkers and treatments?
Our lab analysis showed that our FIRES patient who responded to anakinra has mutations in her IL-1 receptor that are associated with ulcerative colitis and rheumatoid arthritis, as well as some novel IL-1 receptor mutations. We also found that she was making more IL-1 isoform, especially in her cerebrospinal fluid, than other individuals — but the isoform was defective. Our current hypothesis for why this child responded so robustly to anakinra is that she has a functional deficiency in IL-1 receptor antagonist function that anakinra replaced. That suggests that other children with autoinflammatory disease might be screened for a functional IL-1 deficit to help determine if anakinra would be an effective treatment.

In addition to analyzing patient samples, we are using animal models to study the cytokines associated with seizures. That work focuses primarily on TNF because we have a lot of lab-based evidence of how TNF can alter neurocircuity.

Q: What role do you foresee autoinflammatory disease playing in future diagnosis and treatment of people with refractory epilepsy?
Currently, about 30 percent of all patients with epilepsy do not respond completely to anti-seizure medications. Many of these children and adults will have anti-inflammatory therapy to treat their seizure disorders — and not just people with rare disorders such as FIRES. We know that increased seizure burden can potentiate inflammation in and of itself.

Our research has given us some evidence of a commonality in the changes that occur in the inflammatory profiles of people before they experience seizures. Something may cause the release of the factors that can recruit the innate immune cells into the brain and cause the seizure. In our animal models, we have successfully intervened to block these factors and prevent seizures.

Currently, we use anti-seizure medications like a hammer, to knock the seizures down. Cytokine analysis can result in precision therapy that targets a specific pathway and addresses ongoing inflammation. Our ultimate hope is that, even if someone has had epilepsy for 40 years, we can find an inflammatory component and successfully target it. The goal of Mayo Clinic’s lab research is to impact human health.
Research Highlights in Neurology and Neurosurgery

DIA/DIG Outcomes Correlate to Tumor Location
Desmoplastic infantile astrocytoma (DIA) and desmoplastic infantile ganglioglioma (DIG) are rare, benign central nervous system tumors that typically present within the first two years of life. Classically, patients present with a rapidly enlarging head circumference. Resection is typically curative; the prognosis is generally good, with long disease-free survival. In light of reportedly similar clinical, radiological and pathological features, DIA and DIG are categorized together and designated grade I in the 2016 World Health Organization classification. But there have been reports of patients with atypical presentations of DIA/DIGs who may have markedly different clinical courses and long-term outcomes. A study of patients treated for DIA/DIGs at Mayo Clinic has identified two subgroups, based on tumor location. Data of seven patients with histopathology-proven DIA/DIGs and preoperative imaging were retrospectively reviewed. Age, sex, clinical presentation, imaging characteristics, tumor location, surgical procedure, postoperative morbidity and overall mortality were recorded. Four patients had tumors in the cerebral hemispheres, and three had lesions in the suprasellar region. The Mayo researchers found that patients with suprasellar disease experienced ocular abnormalities, including nystagmus and a preference for downward gaze. These patients also experienced significant postoperative complications and had poor long-term outcomes. In contrast, patients with hemispheric tumors underwent more-extensive resection and had uneventful postoperative courses with no documented long-term comorbidities. The research is the first direct comparison of the clinical course of patients with suprasellar tumors and classically described hemispheric disease. (Naylor RM, et al. Novel suprasellar location of desmoplastic infantile astrocytoma and ganglioglioma: A single institution’s experience. Journal of Neurosurgery: Pediatrics. 2018;22:397.)

Independent Association Between APOE e4 and Lewy Bodies Pathology
The APOE e4 allele has been associated with an increased risk of Lewy body disease, although the causal mechanism hasn’t been elucidated. Many people with Lewy body disease also have Alzheimer’s pathology. Mayo Clinic researchers have found that APOE e4 is associated with a greater severity of Lewy bodies pathology independently of Alzheimer’s disease pathology. The researchers genotyped 652 autopsy-confirmed cases of Lewy body disease and 660 controls for APOE e4. In case-control analysis, Lewy body disease cases were classified into nine groups according to severity of both Lewy bodies pathology and Alzheimer’s disease pathology. In the Lewy body disease, the researchers also measured Lewy body counts from five cortical regions, and evaluated associations with APOE e4 according to the severity of Alzheimer’s disease pathology. As expected, APOE e4 was associated with an increased risk of transitional and diffuse Lewy body disease in cases with moderate or high Alzheimer’s disease pathology. However, APOE e4 was also associated with an increased risk of diffuse Lewy body disease in cases with low Alzheimer’s disease pathology. In the Lewy body disease subgroup with low Alzheimer’s pathology, APOE e4 was associated with significantly more Lewy body counts in the five cortical regions. The results suggest that APOE e4 might function as a modifier of processes that favor Lewy bodies spread rather than acting directly to initiate Lewy bodies pathology. (Dickson DW, et al. APOE e4 is associated with severity of Lewy body pathology independent of Alzheimer pathology. Neurology. 2018;91:e1182.)

Obstructive Sleep Apnea and Refractory Epilepsy
People with epilepsy are at 20 times greater risk of sudden death than are people in the general population. The mechanisms underlying sudden unexpected death in epilepsy (SUDEP) remain largely undefined, although several risk factors have been identified. In a pilot study, Mayo Clinic researchers found a relatively high frequency of probable obstructive sleep apnea (pOSA) in people with refractory epilepsy. The researchers prospectively recruited 49 consecutive adult patients admitted to Mayo Clinic’s Epilepsy Monitoring Unit with focal, generalized or unclassified epilepsy syndromes. The epilepsy patients were evaluated for OSA, and patients with and without pOSA were compared. Among the patients studied, 35 percent had pOSA. Patients with pOSA were older and heavier, and more frequently had a focal epilepsy syndrome and longer epilepsy duration. The researchers suggest that identification and treatment of obstructive sleep apnea in patients with epilepsy could conceivably provide a novel approach toward lowering the risk of SUDEP; although future studies with polysomnography are needed to confirm predictive features and to determine whether obstructive sleep apnea is associated with SUDEP risk. (McCarter AR, et al. Obstructive sleep apnea in refractory epilepsy: A pilot study investigating frequency, clinical features, and association with risk of sudden unexpected death in epilepsy. Epilepsia. 2018;59:1973.)

To read more about Mayo Clinic neurosciences research and patient care, visit http://www.MayoClinic.org /medical-professionals.
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2019 courses

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Mayo Clinic Multiple Sclerosis and Autoimmune Neurology 2019
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Feb. 24-March 2, 2019
The Ritz-Carlton Amelia Island, Amelia Island, Fla.

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March 1-3, 2019
Mayo Clinic Franke Education Center, Phoenix

2nd Annual Mayo Clinic Advances and Innovations in Complex Neuroscience Patient Care: Brain and Spine 2019
March 7-9, 2019
Enchantment Resort, Sedona, Ariz.

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Mayo Clinic Neurosurgery Updates Symposium 2019
April 4-6, 2019
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Mayo Clinic Clinical Autonomic Quantitation Workshop 2019
April 26-27, 2019
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8th Quadrennial International Conference on Vestibular Schwannoma and Other CPA Tumors: Advancing Care through Ideas and Innovation 2019
June 18-21, 2019
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July
Neurology in Clinical Practice 2019
July 18-21, 2019
Hilton Hawaiian Village Waikiki, Honolulu

November
Convergence Neuroscience 2019
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The Ritz-Carlton, St. Thomas, U.S. Virgin Islands

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Nov. 15-16, 2019
Mayo Clinic Franke Education Center, Phoenix

Mayo Clinic Multidisciplinary Spine Care Conference 2019
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2020 course

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