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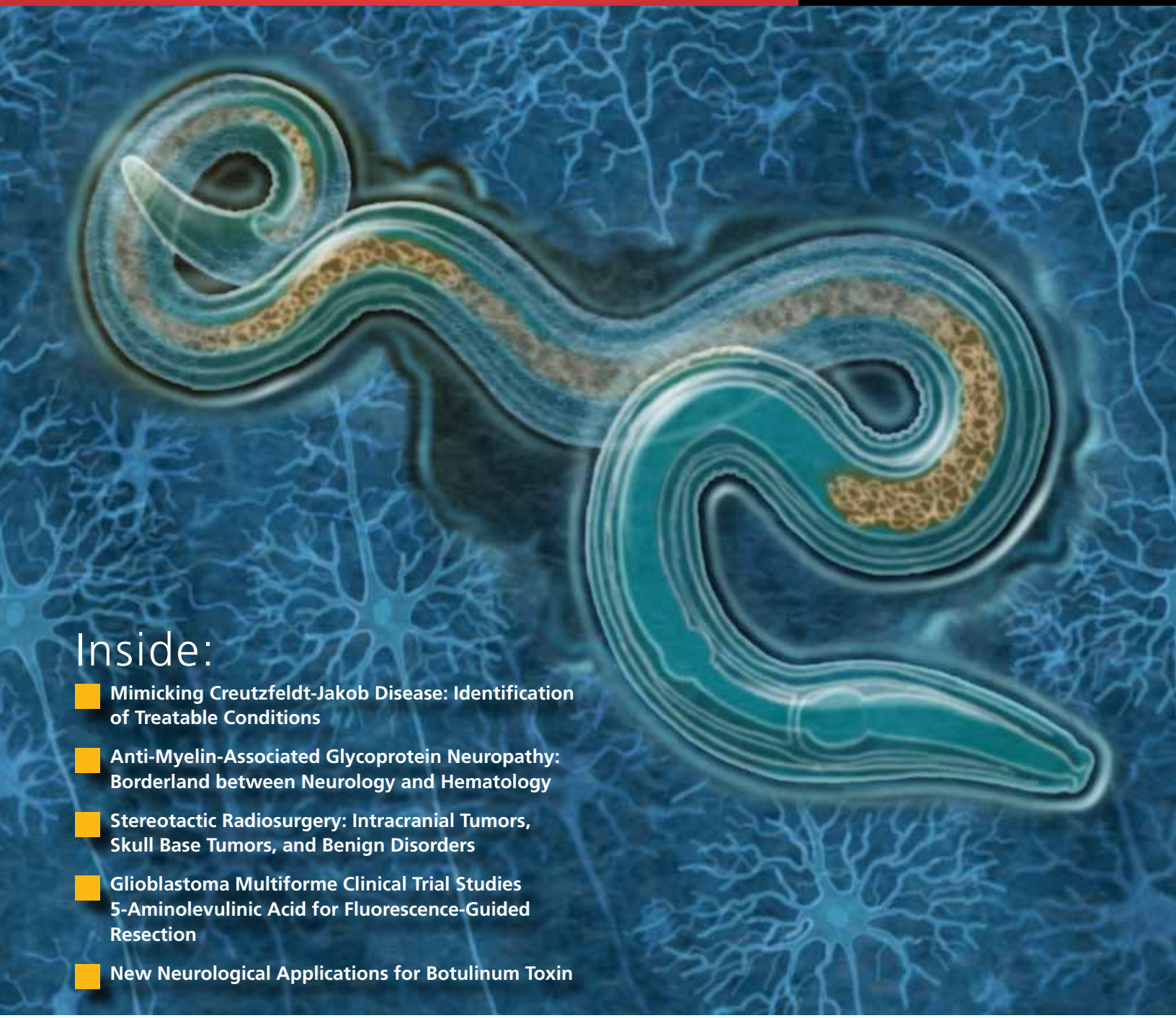
UH Neurological Institute Journal



Inside:

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UH Neurological Institute Journal

FROM THE EDITOR

Dear Colleague,

I am pleased to bring you the Winter 2012 issue of the UH Neurological Institute Journal.

Through continuing collaboration with scientists at Case Western Reserve University School of Medicine, physicians at the UH Neurological Institute test and refine the latest advances in treatment for patients with disabling neurological disorders. The NI Journal highlights these advances and demonstrates our interdisciplinary strengths. As an added benefit for our readers, CME credit is available for the busy practitioner interested in receiving *AMA PRA Category 1 Credits*™.

This issue begins with an investigation of prion disease. Numthip Chitravas, MD, and colleagues present the spectrum of neurological diseases prompting referral to the National Prion Disease Pathology Surveillance Center at Case Western Reserve University and how false-positive diagnoses of progressive cognitive deterioration as Creutzfeldt-Jakob disease may result in failure to provide therapy for potentially treatable neurological disorders.

Tanzila Shams, MD, and colleagues present the case of a patient with anti-MAG neuropathy. With a thorough review of patient data, clinicians can proceed to appropriate cost-effective investigations and, ultimately, to effective treatment. One approach in particular seems to be the most promising.

Simon Lo, MD, and colleagues provide an overview of stereotactic radiosurgery for intracranial tumors as well as benign disorders. As a collaborative effort among radiation oncologists, neurosurgeons, physicists, radiation therapists, and nurses, interdisciplinary care is key to successfully treating these conditions and advancing the available options.

However, in the treatment of glioblastoma multiforme, the past three decades have shown few advances. David Dean, PhD, and colleagues hypothesize that the use of 5-ALA in fluorescence-guided resection may lead to progression-free survival in patients with these brain tumors. The authors review past clinical studies and outline the goals of their recently FDA-approved studies using this agent.

Our issue concludes with an update on botulinum toxin. Used by neurologists for decades to treat a host of neurological conditions, the FDA has recently approved new indications for onabotulinumtoxinA. In their article, Stephen Gunzler, MD, and David Riley, MD, explore its use for the management of chronic migraine headache and upper limb spasticity.

We appreciate your interest in the UH Neurological Institute Journal and welcome your comments and suggestions for future issues. Again we send a special thank you to our authors, without whom there would be no NI Journal.

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University Hospitals Neurological Institute

Recognized by U.S.News & World Report as one of the nation's finest neuroscience programs, University Hospitals Neurological Institute delivers innovative, integrated and individualized care to patients with diseases affecting the nervous system.

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BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL NEUROLOGY & NEUROSURGERY 2011-12

On the cover: Baylisascaris infection in the brain, one of many disorders that may mimic Creutzfeldt-Jakob disease. Read more about this case in the article by Numthip Chitravas, MD, and colleagues on page 2. (Illustration by Ravin Art & Design.)

Kim Duvall, *Editorial Manager*
Bryan Kokish, *Marketing Manager*
Susan Miazga, *Senior Graphic Designer*

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SCHOOL OF MEDICINE CASE WESTERN RESERVE UNIVERSITY

The commitment to exceptional patient care begins with revolutionary discovery. University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a national leader in medical research and education and consistently ranked among the top research medical schools in the country by U.S.News & World Report. Through their faculty appointments at the Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.

Mimicking Creutzfeldt-Jakob Disease: Identification of Treatable Conditions

By
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Introduction: What is Prion Protein? What are Prion Diseases?

The prion protein is a membrane-anchored neuronal glyocoprotein of uncertain function but thought to be involved in long-term memory.[1] Prion diseases are disorders of protein conformation, the most common of which in humans is Creutzfeldt-Jakob disease (CJD). The spectrum of prion disease includes sporadic CJD (sCJD), familial CJD, Gerstmann-Straussler-Scheinker disease, fatal familial insomnia, and acquired (variant and iatrogenic CJD) forms.[2] Sporadic CJD accounts for about 85 percent of cases, and nearly all of the remaining cases are familial secondary to mutations in the prion protein gene.

Prion disease is rare and considered to be a "one in a million" worldwide incidence. CJD is caused by the conversion of the normal endogenous isoform of prion protein (PrPc) into the disease-causing isoform (PrPSc), which is hyperstable (resistant to protease digestion) and, under certain conditions, transmissible. When PrPSc spontaneously arises or is introduced into a healthy brain, it induces the normal, predominantly alpha-helical PrPc to transform into a pathologic, predominantly beta-sheeted form. Similar to the fictional "Ice-nine" of Kurt Vonnegut's *Cat's Cradle*, the misshaped protein then initiates an autocatalytic transformation cascade – a chain reaction – of PrPc to PrPsc conversion, resulting in neuronal death with spongiform degeneration and astrocytic gliosis (Figure 1). This conformational transformation is not recognized by the body as foreign, and hence CJD is not accompanied by an inflammatory reaction, even when it occurs as a result of infection.

Typical symptoms of CJD include rapidly progressive dementia, myoclonus, and other nonspecific symptoms, such as weight loss and malaise.[3] Diagnosis of CJD can be difficult, especially in the early stage. The current World Health Organization (WHO) criteria for diagnosis of CJD are widely utilized to clinically categorize patients into probable and possible CJD (Table 1).[4] However, these criteria have been criticized by experts in the cognitive and behavioral fields because of their lack of specificity. Furthermore, because of the notoriety

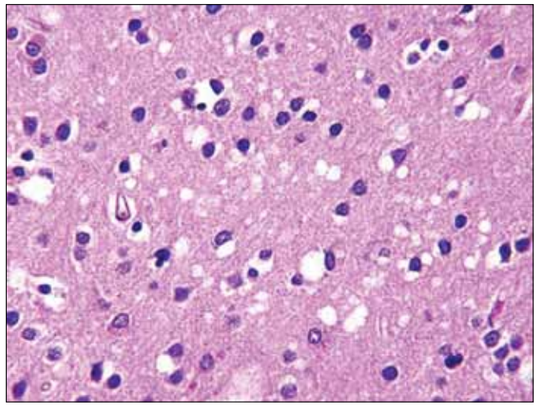

Figure 1: Histopathology of prion-infected brain.

garnered by prion diseases as a result of bovine to human transmission in Britain ("mad cow disease"), clinicians often suspect CJD in any patient with rapidly progressive, unexplained dementia.

Most patients with CJD die within a year of onset.[5] There is no known effective therapy for CJD. As CJD is widely recognized as a "death sentence," which may influence subsequent management of such patients, it is critically important to exclude potentially treatable conditions before making this diagnosis.

The National Prion Disease Pathology Surveillance Center (NPDPSC) at Case Western Reserve University was established in the Division of Neuropathology in 1997. With the support and cooperation of the Centers for Disease Control and the National Institutes of Health, the NPDPSC assists clinicians and pathologists across the United States in analyzing autopsied brain tissue from patients with suspected prion disease. Since its inception, it was clear to researchers at NPDPSC that many specimens they received were from patients who had not died from prion disease. As clinicians, we sought to elucidate the spectrum of neurologic diseases prompting referral to the NPDPSC.

What Mimics Prion Disease? Are These Mimics Treatable?

Prior studies from other prion disease referral centers suggested that the most common non-prion diseases causing rapidly progressive dementia were neurodegenerative disorders, most commonly Alzheimer disease, vascular dementia, frontotemporal dementia, and dementia with Lewy bodies.[6-9] However, other more treatable disorders such as Hashimoto encephalitis, toxic or metabolic encephalopathies, and cerebral lymphoma were also identified.[7-9] These studies were relatively small and had limited numbers of pathologically proven diagnoses; therefore, the number of patients with potentially treatable diseases appeared insignificant.

The large NPDPSC database provided the opportunity to clarify the frequency of non-prion disorders masquerading as CJD. We conducted a retrospective review of pathological findings in autopsied brain tissue received at the NPDPSC from January 2006 to December 2009. Of 1,106 brain autopsies reviewed, a third of cases were negative for prion disease (Figure 2).[10]

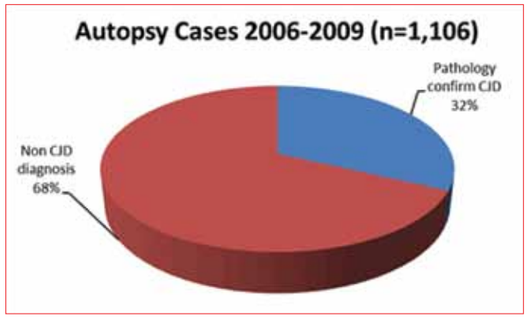

Figure 2: Results from our retrospective review of pathological findings in autopsied brain tissue from cases of Creutzfeldt-Jakob disease (CJD).[10]

Of these 351 prion-negative brains, neurodegenerative diseases accounted for two-thirds of cases, of which Alzheimer disease (50 percent) and vascular dementia (12 percent) were the most common. The findings shown in Table 2 corroborated those reported in previous autopsy studies.[6,9,11-14]

Table 1. World Health Organization criteria for the diagnosis of sporadic Creutzfeldt-Jakob disease (CJD)[4]

Criteria	
I	Rapidly progressive dementia
IIA	Myoclonus
B	Visual or cerebellar problem
C	Pyramidal or extrapyramidal features
D	Akinetic mutism
IIIA	Typical EEG
B	Positive cerebrospinal fluid 14-3-3

Possible CJD: I and 2 of II and duration less than 2 years
Probable CJD: I and 2 of II and IIIA or possible CJD and IIIB
Definite CJD: Neuropathologically confirmed diagnosis

Table 2. Diseases reported mimicking Creutzfeldt-Jakob disease that are untreatable[7,8]

Alzheimer disease
Vascular dementia
Frontotemporal dementia
Mesial temporal sclerosis
Diffuse Lewy body disease
Progressive supranuclear palsy
Corticobasal ganglionic degeneration
Other tauopathy
Huntington disease
Familial spastic paraplegia
Hereditary diffuse leukoencephalopathy with spheroids
Adult polyglucosan body disease
Marchiafava-Bignami disease
Superficial siderosis
Unspecified degenerative brain disease

Table 3. Diseases mimicking Creutzfeldt-Jakob disease for which treatment is available[10]

Total number of brains autopsied	**n = 71**
Immune mediated disorders	**26**
14-3-3 positive (8 of 26)	
Primary angiitis of the CNS	7
Acute disseminated encephalomyelitis	6
Limbic encephalitis	6
Neurosarcoidosis	4
Paraneoplastic cerebellar degeneration	2
Wegener granulomatosis	1
CNS neoplasms	**25**
14-3-3 positive (7 of 25)	
Primary CNS lymphoma	8
Intravascular lymphoma	8
Leptomeningeal lymphoma	2
Malignant glioma	5
Leptomeningeal carcinomatosis	2
CNS infections	**14**
14-3-3 positive (9 of 14)	
Fungal infection	
Coccidioides immitis	3
Aspergillus fumigates	1
Cryptococcus neoformans	1
Viral meningoencephalitis	5
Parasitic infestation	
Round worms	2
Other parasitic infection	2
Metabolic or toxic encephalopathies	**6**
14-3-3 positive (4 of 6)	
Wernicke encephalopathy	3
Other metabolic disorders	3

CNS = central nervous system

Table 4. Clinical features of patients misdiagnosed with Creutzfeldt-Jakob disease for whom treatment was available[10]

Median age in years (minimum to maximum)	**65 (23–87)**
Median duration of illness (months)	3 (0.5–16)
Sex (male)	55%
Symptoms	**(Total n = 71)**
Dementia	42
Myoclonus	12
Cerebellar	14
Visual	9
Pyramidal	20
Extrapyramidal	12
Akinetic mutism	5
Psychiatric*	17
Seizure	10
Available cerebrospinal fluid 14-3-3 protein results	**n = 56**
Positive	29
Negative	27
Available EEG results	**n = 21**
Typical**	1
Diffuse generalized slowing pattern	17
Normal	3

**Psychiatric symptoms include auditory and visual hallucination, depression, and delusion.*

***Typical EEG is 1-Hz focal or diffuse periodic lateralizing epileptiform discharges.*

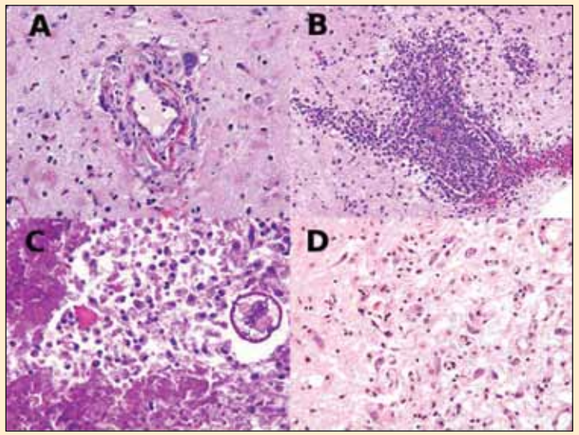

Figure 3: Representative cases of patients with treatable disorders who were misdiagnosed with Creutzfeldt-Jakob disease: (A) primary CNS angiitis, (B) primary CNS lymphoma, (C) Baylisascaris infection, and (D) Wernicke encephalopathy.

We also identified 71 patients who died from potentially treatable prion mimics; Table 3 lists their diagnoses, and Table 4 provides demographic data and clinical features. We divided these cases into four categories: immune-mediated disorders, central nervous system (CNS) neoplasms, CNS infections, and metabolic disorders. The median age of these patients was 65 (23–87) years, median disease duration was three months (0.5–16), and 55 percent were male. Only 11 percent met WHO diagnostic criteria for "probable" sCJD, and 18 percent met criteria for "possible" sCJD. Of these 71 patients with potentially treatable disorders, 42 had dementia, 12 had myoclonus, 20 demonstrated pyramidal symptoms, 12 exhibited extrapyramidal symptoms, 14 showed cerebellar dysfunction, nine had visual disturbances, and five developed akinetic mutism. Only one out of 21 available electroencephalography (EEG) reports demonstrated 1-Hz focal or diffuse periodic epileptiform discharges typically seen in patients with CJD. However, more than half of the available cerebrospinal fluid (CSF) results revealed positive CSF 14-3-3 protein.

Illustrative Cases Misdiagnosed as CJD

Highlighting the spectrum of disorders that may mimic CJD, Figure 3 provides one example from each category of misdiagnosis. Panel A shows granulomatous arteriolar inflammation indicative of primary CNS angiitis from the thalamus of an 85-year-old woman who presented with cognitive decline, lower limb weakness, myoclonic jerks, and an EEG showing diffuse generalized slowing. Panel B shows primary CNS lymphoma in the thalamus from a 68-year-old woman with progressive memory decline, personality change, limb and gait ataxia, and magnetic resonance imaging (MRI) showing periventricular white matter changes; CSF cytology and flow cytometry were negative. Panel C shows necrotizing eosinophilic meningoencephalitis containing roundworms with lateral spines consistent with *Baylisascaris* infection from a 54-year-old man who presented with rapid cognitive decline and spastic paraparesis and underwent cervical decompression without improvement. His MRI eventually showed bilateral thalamic and frontal hyperintensity. Panel D shows spongiform degeneration with neuronal sparing in the mamillary body, typical of Wernicke encephalopathy, from a 58-year-old woman who had undergone gastric bypass surgery followed by abdominal pain, nausea, vomiting, weight loss, and cognitive decline, dying within three months of presentation.

How Can We Improve the Diagnostic Accuracy of Prion Disease?

Though widely used to aid diagnosis of sCJD, the WHO criteria were developed to aid postmortem diagnosis in epidemiological studies when pathological diagnosis is not available (Table 1). Thus, the WHO criteria are clinically limited and not appropriate for early diagnosis of sCJD. The diagnostic utility of CSF biomarkers including 14-3-3 protein, neuron-specific enolase, S100 beta, and total tau protein is controversial,[15,16] and our results indicate that they are not reliable unless used in a careful clinical diagnostic context. In our data, more than 50 percent of patients with treatable dementias had a positive CSF 14-3-3 protein test.

Recently, new MRI techniques including diffusion-weighted imaging (DWI) and apparent diffusion coefficient MRI have been reported to improve the sensitivity and specificity of sCJD diagnoses.[17] Neuroimaging findings that may support the diagnosis of CJD include high signal abnormalities on DWI or Fluid Attenuated Inversion Recovery (FLAIR) in the striatum or in at least two cortical regions of the temporal, parietal, and occipital lobes (Figure 4), supporting current recommendations that imaging be incorporated into diagnostic criteria for sCJD.

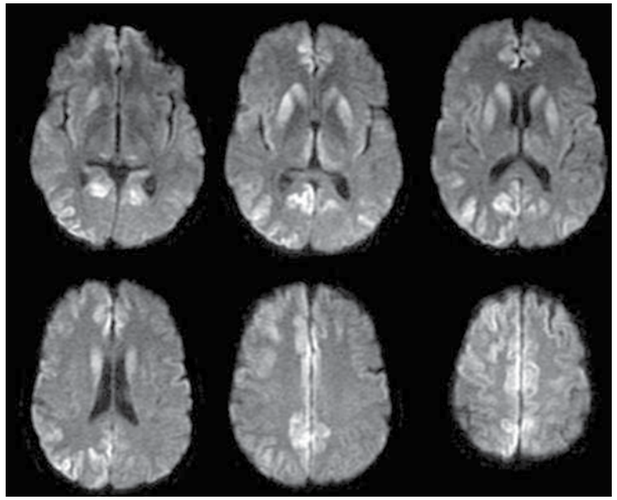

Figure 4: Typical magnetic resonance image (MRI) findings in sporadic Creutzfeldt-Jakob disease (sCJD). Typical diffusion-weighted MRI abnormality in a patient diagnosed with sCJD demonstrates an increased signal in bilateral medial frontal, parietal, and occipital cortices and deep gray matter (particularly the bilateral caudate and putamen).

Conclusion

Our study revealed that a third of all autopsy referral cases were negative for suspected prion disease. Our study largely corroborates the findings of other studies regarding incorrect diagnoses of sCJD.[8,9,12] However, we were also able to elaborate the largest differential diagnosis of prion disease mimics to date. Our most important finding was that a substantial number of patients whose brains had been sent to the NPDPSC with a clinical diagnosis of possible CJD harbored potentially treatable diseases.

Variable and delayed clinical manifestations, the low sensitivity of EEG,[18,19] nonspecifically elevated CSF 14-3-3 protein,[19,20] and the anticipatory concern of worried families may have contributed to physicians' decisions to consider a presumptive diagnosis of sCJD. As a consequence, these factors may have led to early withdrawal of care when patients deteriorated. The misidentification of potentially treatable and, in some cases, reversible diseases as futile, rapidly progressive dementias raised our concern.

Revision of CJD diagnostic criteria is necessary to aid in the early diagnosis of sCJD and to comprehensively rule out treatable causes of rapidly progressive dementia. The clinical criteria for sCJD were first formulated 30 years ago by Masters and colleagues.[21] Recently, these criteria have been re-examined by Zerr and colleagues,[17] who report a sensitivity of 92 percent and specificity of 71 percent. Zerr and colleagues also suggest that incorporating specific MRI brain imaging studies as well as using surrogate biomarkers in the CSF as additional criteria may improve the accuracy of the sCJD diagnosis.[17] As our study indicates, false-positive diagnoses of rapidly progressive cognitive deterioration as CJD may result in failure to recognize and institute therapy for potentially treatable neurological disorders.

We hope that our analysis of a large data set will prompt clinicians to consider a broad spectrum of differential diagnoses in cases suspicious for CJD, apply more reliable diagnostic criteria, and implement appropriate investigations so that those patients with treatable disorders can be identified and appropriately managed.

Pierluigi Gambetti, MD, is a member of the Advisory Committee for Ferring Pharmaceuticals, though this relationship has not affected the content of this article; Dr. Gambetti's contribution to this article includes discussion of unlabeled/investigational uses of a commercial product. The other authors report no financial relationships with commercial interests relevant to the content of this article.

References

1. Shorter J, Lindquist S. Prions as adaptive conduits of memory and inheritance. Nat Rev Genet 2005;6(6):435-450.
2. Gambetti P, Kong Q, Zou W, Parchi P, Chen SG. Sporadic and familial CJD: classification and characterisation. Br Med Bull 2003;66:213-239.
3. Rabinovici GD, Wang PN, Levin J, et al. First symptom in sporadic Creutzfeldt-Jakob disease. Neurology 2006;66(2):286-287.
4. World Health Organization publications. Global surveillance, diagnosis and therapy of human transmissible spongiform encephalopathies: report of a WHO consultation. www.who.int/csr/resources/publications/bse/WHO_EMZ_ZDI_98_9/en/. Accessed July 22, 2010.
5. Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol 1999;46(2):224-233.
6. Van Everbroeck B, Dobbeleir I, De Waele M, De Deyn P, Martin JJ, Cras P. Differential diagnosis of 201 possible Creutzfeldt-Jakob disease patients. J Neurol 2004;251(3):298-304.
7. Gelpi E, Heinzl H, Hoftberger R, et al. Creutzfeldt-Jakob disease in Austria: an autopsy-controlled study. Neuroepidemiology 2008;30(4):215-221.
8. Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL. Rapidly progressive dementia. Ann Neurol 2008;64(1):97-108.
9. Poser S, Mollenhauer B, Kraubeta A, et al. How to improve the clinical diagnosis of Creutzfeldt-Jakob disease. Brain1999;122(Pt 12):2345-2351.
10. Chitravas N, Jung RS, Kofskey DM, et al. Treatable neurological disorders misdiagnosed as Creutzfeldt-Jakob disease. Ann Neurol 2011;70(3):437-444.
11. Heinemann U, Krasnianski A, Meissner B, et al. Creutzfeldt-Jakob disease in Germany: a prospective 12-year surveillance. Brain 2007;130(Pt 5):1350-1359.
12. Josephs KA, Ahlskog JE, Parisi JE, et al. Rapidly progressive neurodegenerative dementias. Arch Neurol 2009;66(2):201-207.
13. Tschampa HJ, Neumann M, Zerr I, et al. Patients with Alzheimer's disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 2001;71(1):33-39.
14. Zerr I, Poser S. Clinical diagnosis and differential diagnosis of CJD and vCJD. With special emphasis on laboratory tests. Apmis 2002;110(1):88-98.
15. Burkhard PR, Sanchez JC, Landis T, Hochstrasser DF. CSF detection of the 14-3-3 protein in unselected patients with dementia. Neurology 2001;56(11):1528-1533.
16. Chohan G, Pennington C, Mackenzie JM, et al. The role of cerebrospinal fluid 14-3-3 and other proteins in the diagnosis of sporadic Creutzfeldt-Jakob disease in the UK: a 10-year review. J Neurol Neurosurg Psychiatry 2010;81(11):1243-1248.
17. Zerr I, Kallenberg K, Summers DM, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Brain 2009;132(Pt 10):2659-2668.
18. Steinhoff BJ, Zerr I, Glatting M, Schulz-Schaeffer W, Poser S, Kretzschmar HA. Diagnostic value of periodic complexes in Creutzfeldt-Jakob disease. Ann Neurol 2004;56(5):702-708.
19. Zerr I, Pocchiari M, Collins S, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. Neurology 2000;55(6):811-815.
20. Satoh J, Kurohara K, Yukitake M, Kuroda Y. The 14-3-3 protein detectable in the cerebrospinal fluid of patients with prion-unrelated neurological diseases is expressed constitutively in neurons and glial cells in culture. Eur Neurol 1999;41(4):216-225.
21. Masters CL, Harris JO, Gajdusek DC, Gibbs CJ, Jr., Bernoulli C, Asher DM. Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. Ann Neurol 1979;5(2):177-188.

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Anti-Myelin-Associated Glycoprotein Neuropathy: Borderland between Neurology and Hematology

By
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A 70-year-old man with a three-year history of progressive gait ataxia and numbness was referred to our Neuromuscular Center by his local neurologist for evaluation of possible Charcot-Marie-Tooth (CMT) disease. He initially noted unsteadiness of gait that was prominent with eyes closed; it gradually worsened to the point of requiring support while walking. He suffered frequent falls and required aid with basic activities of daily living, such as standing in a shower. One year after the onset of imbalance, he noted hypoesthesia in bilateral hands and feet as well as mild weakness in his lower extremities, which was most prominent while climbing stairs. He also noted mild resting tremor of the left hand, which did not progress over time. Past medical history included hypertension, dyslipidemia, and tobacco abuse. There was no pertinent family history of similar symptoms, including ataxia and peripheral neuropathy.

At the time of presentation, general examination of the lymph nodes, chest, abdomen, and extremities was unremarkable. Neurological examination revealed intact cognition and cranial nerves, and the patient had no pes cavus, hammer toes, claw hands, or scoliosis. Motor examination showed symmetric, mild, decreased strength in bilateral proximal lower extremities (4+/5 bilateral hip flexors) but normal power in all other muscle groups. Areflexia was noted as was a pill-rolling resting tremor in the left hand. Sensory examination revealed intact light touch and pain sensation, with marked loss of vibration and impaired joint position sense in bilateral hands and feet to the ankle joints. Gait was ataxic with positive Romberg sign.

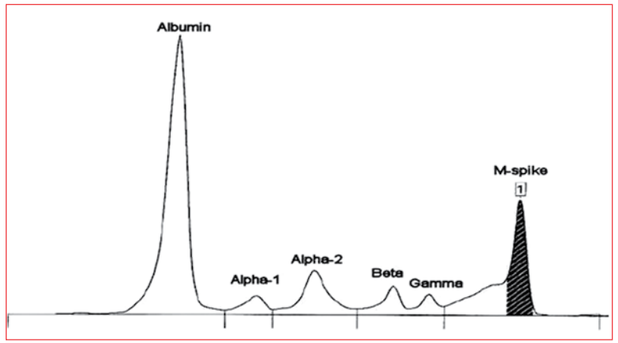

Figure 1: Urine protein electrophoresis displaying IgM Kappa monoclonal spike. M-spike = monoclonal spike

Electromyography studies revealed a moderately severe sensorimotor demyelinating peripheral polyneuropathy, with symmetric significant slowing of conduction velocities ranging from 11–28 meters per second in all nerves tested in upper and lower extremities without any conduction block. A needle study showed chronic neurogenic changes, with occasional fibrillation potentials.

Upon further work-up for demyelinating peripheral neuropathy, serum protein electrophoresis showed IgM kappa monoclonal spike measuring 1.1 gm/dL (Figure 1). Urine protein electrophoresis revealed monoclonal free kappa light chain in the urine. The patient's anti-myelin-associated glycoprotein (anti-MAG) was significantly elevated with a titer of 1:1,638,400 (normal less than 1:1600). Sulfate-3-Glucuronyl Paragloboside (SGPG) antibody was also elevated at 1:102,400 (normal less than 1:3200).

Table 1: Work-up Differentiating Benign Monoclonal Gammopathy of Undetermined Significance from Malignant Plasma Cell Disorders

Benign	Malignancy
• < 3g/dL of monoclonal protein in serum and rarely the same monoclonal protein in urine • < 5% plasma cells in bone marrow aspirate • No signs of renal insufficiency, anemia, hypercalcemia, negative bone survey • No suppression of background immunoglobulins • Stable monoclonal proteins on follow-up	• Lytic bone lesions on bone survey • Bence-Jones proteinemia • Decreased background immunoglobulins • Abnormal bone marrow examinations • Progressive increase in monoclonal protein in serial measurements

A skeletal survey did not reveal osteolytic or osteosclerotic lesions. Complete blood count and renal function panel were within normal limits. The patient underwent a bone marrow biopsy, which was normal and without evidence of plasma cell dyscrasia. A diagnosis of anti-MAG neuropathy was established, and treatment with intravenous immunoglobulin (IVIG) (5 mg/kg body weight for five days) was started, with plans to monitor for improvement, repeat in four to six weeks, and initiate treatment with rituximab if no positive response was noted.

Discussion

When approaching a patient with peripheral polyneuropathy, we generally suggest a *rational approach* rather than a *shotgun approach*, which is not cost-effective. Pattern recognition is useful but rarely encountered in clinical practice; it applies mostly to very advanced cases of polyneuropathy and may require extensive clinical experience. The rational approach uses data from the history, physical examination, and electrodiagnostic (EDX) testing to determine key information, including temporal profile, anatomic pattern (e.g., distal vs. proximal, symmetric vs. asymmetric), types of nerve fiber involvement (large fiber sensory, small fiber sensory, motor, autonomic, or mixed), and primary pathology (axonal vs. demyelinating). An initial impression can then be formulated, and we can proceed to appropriate cost-effective investigations.

Our patient presented with a three-year history of progressive sensory ataxia, with marked impairment of proprioception and joint position sense without cerebellar features. This presentation reflects large fiber sensory impairment causing "sensory ataxia" rather than cerebellar ataxia. Lesions can be localized to either the posterior column of the spinal cord or large-fiber sensory nerves. Deep tendon reflexes were markedly decreased throughout, and the patient had no signs of myelopathy. Therefore, we were able to localize the lesion at large-fiber sensory nerves. Based on the patient's history, physical examination, and EDX studies, this patient was diagnosed with chronic, slowly progressive, distal acquired demyelinating symmetric (DADS) neuropathy, primarily affecting the large sensory fibers. Although motor weakness was minimal clinically, EDX studies demonstrated motor involvement and motor nerve conduction studies showed marked slowing of conduction velocities, distal latencies, and F-wave latencies. Cumulatively, we were able to deduce that the primary pathology was demyelinating with secondary axonal loss, causing decreased distal compound muscle action potential amplitudes. Importantly, although there was no conduction block, slowing of motor conduction velocities was not uniform, suggesting acquired demyelination rather than inherited demyelination. Also, the patient had no family history of pes cavus or hammer toes, which is suggestive of chronic inherited neuropathy.

On further hematologic studies, our patient, who exhibits the DADS variant of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), had IgM kappa-monoclonal protein in the serum as well as elevated anti-MAG and anti-SGPG. Additional normal studies included a skeletal survey, bone marrow aspiration, blood count, and examination of serum calcium and creatinine levels (Table 1). To exclude multiple myeloma, the following results are required: monoclonal protein less than 3 gm/dL, no lytic bone lesions on skeletal surveys, plasma cells less than 5 percent in bone marrow aspiration, normal hemoglobin levels, normal calcium levels, and normal renal function. Periodic hematologic screening is also needed.

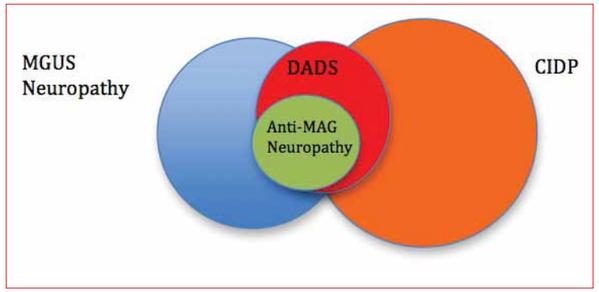

Figure 2: Overlaps between chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), monoclonal gammopathy of undetermined significance (MGUS) neuropathy, and anti-myelin-associated glycoprotein (Anti-MAG) neuropathy.[7] DADS = distal acquired demyelinating symmetric

What is DADS neuropathy?

DADS neuropathy is considered to be a variant of CIDP.[1] The patient usually has very mild, if any, motor symptoms. It is important to recognize DADS neuropathy as it can be associated with paraproteinemia, such as monoclonal gammopathy of undetermined significance (MGUS). MGUS is a condition with monoclonal subtypes of IgM, IgA, or IgG, with IgM-MGUS subtype occurring most frequently.[2] About two-thirds of patients with DADS neuropathy have an IgM paraproteinemia. The majority of them have detectable anti-MAG antibodies. Indeed, CIDP, MGUS neuropathy, and anti-MAG neuropathy are overlapping entities (Figure 2).[3] Patients who have CIDP with MGUS are older and have less response to conventional treatments, such as steroids and IVIG, compared to patients who have CIDP without MGUS (Table 2).[4]

As is the case of our patient, it is not uncommon for this group to be misdiagnosed as demyelinating type of CMT disease or hereditary motor and sensory neuropathy (HMSN), such as HMSN1/CMT1, HMSN3/CMT3, or CMTX (Figure 3), due to the marked slowing of latencies and conduction velocities.[2]

What is anti-MAG?

MAG is a component of nerve cell membrane that is found in the central nervous system (CNS) and peripheral nervous system (PNS). Anti-MAG is essentially IgM paraprotein. However, patients with IgM-MGUS neuropathy do not necessarily have anti-MAG antibodies. Anti-MAG antibodies are found in almost half of patients with IgM neuropathy by Western Blot methodology and in 70 percent of patients by the ELISA method.[5] In anti-MAG neuropathy, MAG, as an antigen, is attacked by anti-MAG IgM paraproteins. The antigenic component of MAG is thought to be the carbohydrate portion; the deglycosylation of MAG leads to loss of the immunoreactivity of the antibody,[6] posing the question of why anti-MAG affects only the PNS despite its presence in the CNS. Actually, the CNS may also be attacked

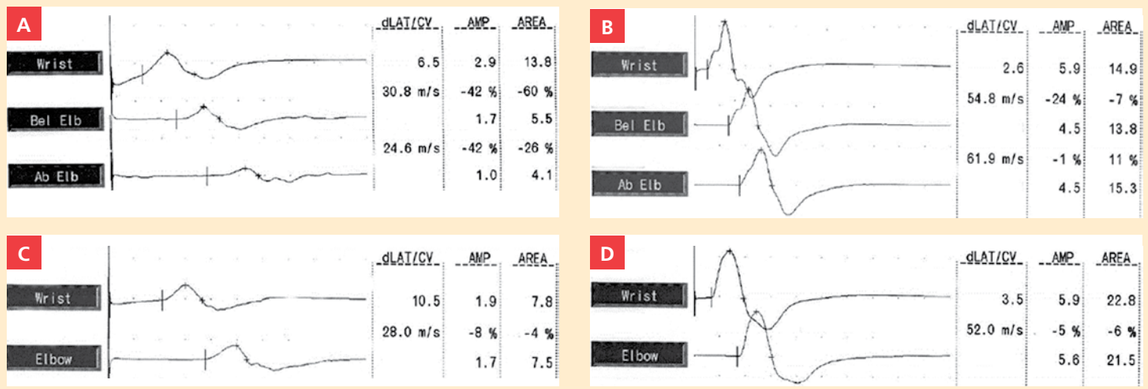

Figure 3: Nerve conduction studies of MGUS Anti-MAG Neuropathy compared to control subject. (A) Compound muscle action potentials (CMAP) of the patient recording from abductor digiti minimi when stimulating left ulnar nerve at the wrist, below and above the elbow. (B) CMAP of the patient recording from abductor digiti minimi of the age-matched normal control when stimulating left ulnar nerve at the wrist, below and above the elbow. (C) CMAP recording from abductor pollicis brevis of the patient when stimulating left median nerve at the wrist and the elbow. (D) CMAP recording from abductor pollicis brevis of the age-matched normal control when stimulating left median nerve at the wrist and the elbow. Ab Elb = above elbow; AMP = amplitude; Bel Elb = below elbow; CV = conduction velocity; dLAT = distal latency; m/s = meters/second

Table 2: Acquired Chronic Demyelinating Polyneuropathies

Condition	Salient Features
Chronic inflammatory demyelinating polyradiculoneuropathies	• Prototype of all chronic acquired demyelinating polyneuropathies • Any age • Relapsing and remitting or slowly progressive over several months • Proximal and distal symmetrical weakness • Numbness and paresthesia in feet and hands • Generalized areflexia
Chronic demyelinating polyneuropathy with anti-MAG antibody	• Predominantly sensory ataxia and distal numbness with or without weakness • Age > 50 • Symmetric • Sensory > motor symptoms • Prominent gait disorder (70%) • Tremor (30%) • 85% of serums with anti-MAG antibodies have IgM monoclonal protein • 50% of IgM monoclonal proteins bind to MAG[11,12]
Chronic demyelinating polyneuropathy with MGUS (IgM, IgG, or IgA)	• MGUS may or may not progress to neoplasm[13] • Risk of progression related to monoclonal protein concentration • Neuropathy occurs in 5-28% of MGUS patients with IgM most common • 50-70% of patients with IgM neuropathy have anti-MAG antibodies
Chronic demyelinating polyneuropathy with osteosclerotic myeloma (POEMS syndrome)	• Required features are monoclonal protein and a polyneuropathy • Paresthesia in feet and hands are usually a presenting feature • 50% of cases have loss of vibration and touch • Hyporeflexia • Hyperhidrosis • Progressive over months to years[14] • Serum monoclonal protein in 75-85% of cases
Chronic demyelinating polyneuropathy with multiple myeloma	• Polyneuropathy • Sensory > motor symptoms • Distal symmetrical sensory loss • Distal weakness legs > arms • More commonly IgG or IgA1[5]

Ig = immunoglobulins; MAG = myelin-associated glycoprotein; MGUS = monoclonal gammopathy of undetermined significance; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes

by anti-MAG IgM paraproteins but to a much lesser extent than the PNS. As opposed to MAG, SGPG, also attacked by anti-MAG IgM protein, is found exclusively in the PNS, which may be the reason anti-MAG IgM paraproteins predominantly affect the PNS rather than the CNS. Electron microscopy shows splitting of outer myelin lamellae, likely secondary to an autoimmune process.[7]

What is Anti-MAG neuropathy?

Our patient had typical presentations of anti-MAG neuropathy. Patients typically have slow progression of symptoms. As opposed to CIDP with MGUS (including anti-MAG neuropathy), CIDP without MGUS may have a progressive or relapsing-remitting clinical course. In anti-MAG neuropathy, sensory symptoms are much more predominant than motor symptoms. Large fibers are predominantly affected, so patients typically present with sensory ataxia. Tremor, which is secondary to neuropathy, is common. Patients typically have minimal or mild, if any, motor symptoms. EDX typically shows symmetric demyelinating sensorimotor neuropathy, affecting the distal more than proximal nerves.

Our patient demonstrated DADS neuropathy with anti-MAG antibodies, considered by some as a variant of CIDP. Neurologists generally differ in opinion when classifying CIDP, and most subscribe to either a "lumpers" or "splitters" approach regarding subtypes (Figure 4). This case highlights the place where "splitting" is helpful and, by correctly defining this entity, we can limit differential diagnoses to guide appropriate cost-effective investigations.[2]

Treatment of Anti-MAG Neuropathy

Initiation of treatment should be based on the severity of symptoms. Sensory ataxia can be very disabling and impair quality of life. Patients may have severe weakness, although most cases of anti-MAG neuropathy manifest as minimal motor symptoms. Even though DADS neuropathy, IgM neuropathy, and anti-MAG neuropathy are considered variants of CIDP, conventional treatments for CIDP, including prednisone and IVIG, are not as effective. Only about half of patients respond to IVIG.[8] Chemotherapeutic agents, such as cladribine, cyclophosphamide, and fludarabine, have been studied, but studies lack adequate sample size.[9] There is also concern for malignant transformation with cyclophosphamide therapy.[10] Fludarabine may cause potential adverse effects, and further randomized-controlled studies will be needed (Table 3).[10]

Rituximab, monoclonal antibody directed against CD20, has been studied and seems to be promising in therapy of anti-MAG neuropathy. One randomized, double-blinded, placebo-controlled study of rituximab in anti-MAG neuropathy was published in 2009.[7] This study has been the only large randomized trial thus far. Twenty-six patients were recruited; 13 were randomized to receive rituximab 375 mg/m2 weekly for four doses; the others were randomized to a placebo group. The study showed improvement of the Inflammatory Neuropathy Cause and Treatment (INCAT) leg disability score of at least 1 after eight months in the rituximab group as compared to the placebo group, which was statistically significant (4/12 patients vs. 0/12 patients, P = 0.036). Of note, one patient was excluded from data analysis because INCAT

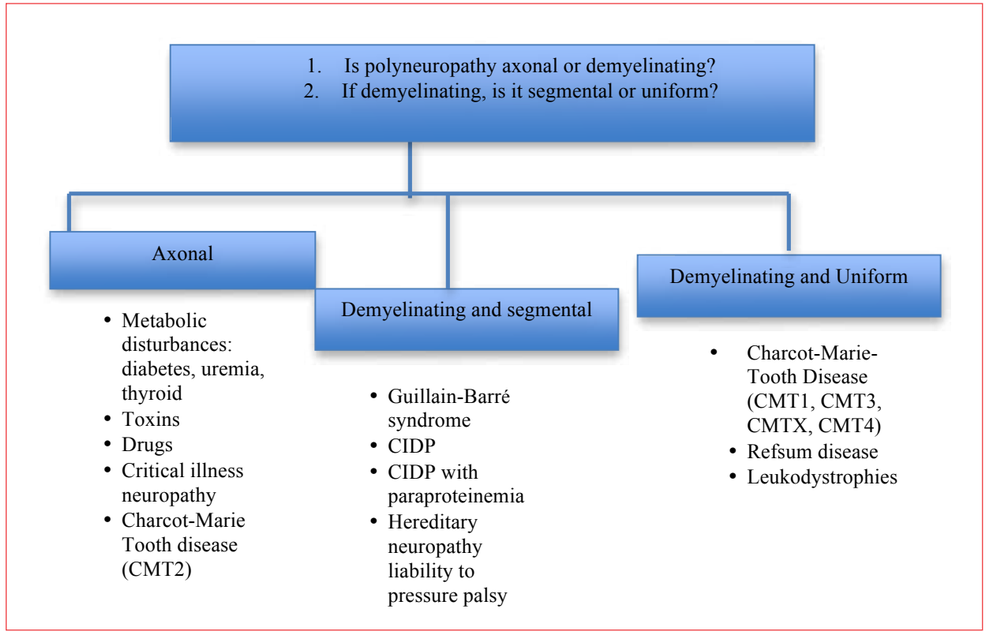

Figure 4: Differentiating primary pathology in polyneuropathy.[7]

Table 3: Treatment options for Anti-MAG neuropathy with existing trials and level of evidence

Therapy	Trial Design	Outcome	Level of Evidence
Chlorambucil and prednisone	Anecdotal (no controlled study to date)	Some improvement of symptoms in Waldenström's macroglobulinemia	Class IV
Cyclophosphamide (combination with prednisolone)	Randomized controlled trial n = 35	Significant improvement of sensory ataxia and quality of life	Class II
Fludarabine	Open label study n = 16	Five patients improved but adverse effects in four patients	Class IV
IVIG	Randomized controlled n = 22	About 50% of patients improved	Class II
Rituximab	Double-blind, placebo-controlled	Significant improvement of symptoms and disability	Class I

IVIG = intravenous immunoglobulin; MAG = myelin-associated glycoprotein

leg disability score was normal at baseline; therefore, improvement from analysis at eight months could not be seen. The 10-meter walk time was significantly reduced in the rituximab group at eight months (P = 0.042).

Seven of 13 patients in the rituximab group showed clinical improvement of walking and daily activities compared to 0 of 13 patients in the placebo group. Immunologically, IgM and anti-MAG titers were decreased by 34 percent and 50 percent at eight months in the rituximab group, respectively. Patients who tended to have better improvement were those who had higher anti-MAG titers and more severe sensory symptoms at baseline. However, one can argue that the INCAT leg disability score assessment tool is primarily a motor scale and the disease entity consists of sensory disabilities. Seven of 13 patients in the rituximab group had clinical improvement of sensory ataxia.

Immunological mechanism of rituximab in anti-MAG neuropathy is not straightforward. Mature plasma cells do not express CD20, but memory B-cells, which are precursors of short-lived plasma cells, do. Rituximab reduces antibody production (IgM and anti-MAG) by depletion of memory B-cells and short-lived plasma cells. It may also induce immunoregulatory T-cells.

Side effects of rituximab include infusion-related reactions, such as transient hypotension and allergic reactions, infections by virus or bacteria, and progressive multifocal leukoencephalopathy (rare). Infusion-related reactions can be treated with methylprednisolone infusion.

Several questions regarding additional treatment after relapse have yet to be answered. There is no clear evidence whether we can retreat with rituximab and what the dose should be. These questions require further studies.

Practical Points

- DADS neuropathy as a variant of CIDP should prompt further investigations for paraproteinemic neuropathy, especially IgM-MGUS and anti-MAG neuropathy.
- DADS neuropathy sometimes can be misdiagnosed as CMT disease, which shows uniform slowing of conduction velocities. Interpretation of EDX testing should be done in good clinical context. Positive family history as well as pes cavus and hammer toes may suggest inherited neuropathy.
- In IgM neuropathy, myeloproliferative disorders, including multiple myeloma, should be ruled out prior to initiation of the treatment.
- Rituximab can improve clinical and immunological profiles in anti-MAG neuropathy.

Conclusion

CIDP can be associated with paraproteinemia, including MGUS. These patients are less responsive to conventional therapies of CIDP, such as steroid or IVIg, than are the patients without MGUS. The DADS variant of CIDP has a strong association with IgM-MGUS. Likewise, some patients with DADS neuropathy and IgM-MGUS also have positive anti-MAG. Of the therapies available to patients with anti-MAG neuropathy, rituximab may be the most promising.

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References

1. Katz JS, Saperstein DS, Gronseth G, et al. Distal acquired demyelinating symmetric neuropathy. Neurology 2000;54:615-620.
2. Katirji B. Electromyography in clinical practice: a case study approach, 2nd ed. Philadelphia: Mosby Elsevier, 2007;275-288.
3. Cocito D, Durelli L, Isoardo G. Different clinical, electrophysiological and immunological features of CIDP associated with paraproteinemia. Actaneurologica Scandinavica 2003;108(4):274-280.
4. Ueda M, Kusunoki S. Autoimmune neuropathies: diagnosis, treatment, and recent topics. Brain Nerve 2011;63(6):549-555.
5. Kuijf ML, Eurelings M, Tio-Gillen AP, et al. Detection of anti-MAG antibodies in polyneuropathy associated with IgM monoclonal gammopathy. Neurology 2009;73:688–695.
6. Ilyas AA, Quarles RH, MacIntosh TD, et al. IgM in a human neuropathy related to paraproteinemia binds to a carbohydrate determinant in the myelin-associated glycoprotein and to a ganglioside. Proceedings of the National Academy of Sciences of the United States of America 1984;81(5):1225-1229.
7. Dalakas MC, Quarles RH. Autoimmune ataxic neuropathies (sensory ganglionopathies): are glycolipids the responsible autoantigens? Annals Neurol 1996;39(4):419-422.
8. Comi G, Roveri L, Swan A, et al. A randomized controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. J Neurol 2002;249:1370-1377.
9. Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. J Periph Nerv Syst 2010;15(10):185-195.
10. Niermeijer JM, Eureligs M, van der Linden MW, et al. Intermittent cyclophosphamide with prednisone versus placebo for polyneuropathy with IgM monoclonal gammopathy. Neurology 2007;69(9):50-59.
11. Keren DF, Warren JS, Lowe JB. Strategy to diagnose monoclonal gammopathies in serum: high-resolution electrophoresis, immunofixation, and kappa/lambda quantification. Clin Chem 1988;11(6):2196-2201.
12. Latov N. Pathogenesis and therapy of neuropathies associated with monoclonal gammopathies. Annals Neurol 1995;37(10):S32-S42.
13. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. NEJM 2002;346(5):564-569.
14. Nakamoto Y, Imai H, Yasuda T, et al. A spectrum of clinicopathological features of nephropathy associated with POEMS syndrome. Nephrol Dial Transplant 1999;14(8):2370-2378.
15. Mohty B, Jean EC, Ibrahim YA, et al. Peripheral neuropathy and new treatments for multiple myeloma: background and practical recommendations. Haematologica 2010;95(8):311-319.

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Stereotactic Radiosurgery: Intracranial Tumors, Skull Base Tumors, and Benign Disorders

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Introduction

For the past several decades, conventional fractionation has been the standard approach for radiotherapy. In the early 1950s, Swedish neurosurgeon Lars Leksell challenged the conventional wisdom of conventionally fractionated radiotherapy and pioneered the concept of stereotactic radiosurgery (SRS), entailing the delivery of a single high-focused dose of radiation to a tumor in a highly conformal fashion with very steep dose gradient. In the late 1960s, the first prototype of Gamma Knife machine was invented in Sweden. Since the introduction of Gamma Knife-based SRS was introduced into clinical practice, it has been used to treat various intracranial lesions with promising results. Subsequently, other devices have been used to deliver SRS with equally promising outcomes.

Technical Aspects

SRS can be delivered with different treatment devices, including a Gamma Knife unit, protons generated from a cyclotron, a modified linear accelerator (LINAC), and a specialized LINAC, such as a CyberKnife® unit. Except when a frameless system is used, a stereotactic head frame is typically fixed to the skull rigidly.
Since the first Gamma Knife device was installed in Sweden's Karolinska Institute in the 1960s, the device has been modified and upgraded. While the previous versions contained 201 cobalt-60 sources, the current version, Perfexion™ (Elekta Instrument AB, Stockolm, Sweden), houses 192 cobalt-60 sources. Gamma rays are emitted from the source, and they converge at the isocenter. The isodose distribution is adjusted by manipulating the plugs of each shot or placing multiple shots of different weighting. The half-life of the Co-60 sources is 5.26 years, and the sources are usually replaced in five to seven years. The advantage of the current model over previous models is the minimal risk of collision when a lesion located in an extreme position is treated. Furthermore, the software available in Perfexion™ allows for inverse planning.

Numerous centers have used an adapted LINAC to deliver SRS. A secondary gantry is added to the LINAC to enhance the accuracy. Treatment planning is accomplished using cones and arcs or intensity modulated radiation therapy. Novalis TX is a specialized LINAC for SRS. The CyberKnife® (Accuray, Sunnyvale, CA) unit has a robotic arm on which a compact LINAC is mounted, and multiple radiation beams are directed to an intracranial or body target volume with image guidance. There are six degrees of freedom. Real-time tracking is provided by two orthogonal X-ray cameras mounted on the ceiling. Reliable bony landmarks in the skull or spine or implant fiducial markers are used for target localization.

Protons have been used to deliver SRS in a limited number of institutions. Proton beam-based SRS carries a dosimetric advantage because of the Bragg peak. The radiation dose falls off abruptly beyond the Bragg peak. Disadvantages include cost and limited availability.

Clinical Applications

SRS has been used for the treatment of various intracranial and skull base benign and malignant tumors as well as benign conditions. Tumors treated with SRS include meningioma, vestibular schwannoma, glomus tumor, pituitary adenoma, craniopharyngioma, skull base chordoma, skull base chondrosarcoma, low-grade glioma, high-grade glioma, ependymoma, and brain metastasis.[1-10] Benign conditions treated with SRS include arteriovenous malformation (AVM), trigeminal neuralgia, and seizures.[11-20]

Benign and Skull Base Tumors

Benign and skull base tumors are typically well demarcated and are therefore ideal targets for SRS. There is abundant experience on the use of SRS – mostly based on Gamma Knife – for the treatment

of meningioma, vestibular schwannoma, and pituitary adenoma.[1,4,5] Data in the literature show excellent local control. A fair amount of data also exists on the use of SRS for other skull base tumors.[1,2,4]

Meningiomas have a sharp demarcation from normal brain parenchyma and are ideal targets for SRS. Data on SRS for the treatment of meningioma show local control rates ranging from 75 percent to 100 percent.[21] The reported complication rates are usually low in modern series. Patients with large meningiomas or meningiomas close to eloquent structures, such as the optic chiasm/nerve and brainstem, are usually deemed not suitable for SRS. Stereotactic radiotherapy using 2–5 fractions or conventional fractionated radiation therapy may be considered for these patients.

Treatment options for vestibular schwannoma include observation, microsurgery, SRS, and fractionated radiotherapy (including stereotactic radiotherapy). Studies comparing microsurgery and SRS show similar tumor control rates between microsurgery and SRS but better preservation of the cranial nerve function with SRS.[22-24] Similar to meningioma, vestibular schwannomas are very well demarcated and are ideal targets for SRS. In a large series of 829 patients at the University of Pittsburgh Medical Center, Gamma Knife-based SRS was associated with a tumor control rate of 97 percent.[25] Recent studies report using a low SRS dose of 12–13 Gy with similarly high rates of local control but with much better hearing preservation and lower rates of injury to V and VII nerves.[25] SRS also appears to be a reasonable treatment for patients with neurofibromatosis type 2 associated vestibular schwannoma. SRS confers a significant advantage over the natural history of the disease. One study reports a tumor control rate of 98 percent.[26]

There is abundant literature on the use of Gamma Knife-based SRS for the treatment of nonfunctioning and secretory pituitary adenomas. The endpoints of treatment, namely tumor control and endocrine cure, are twofold. While various studies show excellent tumor control rates typically above 90 percent, the reported endocrine cure rates are more variable,[5] which may be related to the different endpoints used to define endocrine cure. The reported rates of endocrine cure range from 20 percent to 82 percent for acromegaly, 0 percent to 100 percent for prolactinoma, and 10 percent to 100 percent for Cushing's disease.[5] For nonfunctioning tumors, a dose of 15–20 Gy is usually used compared to 20–30 Gy needed for secretory tumors. The rates of optic neuropathy, permanent cranial nerve (oculomotor, trochlear, abducent, trigeminal) deficits, and new trigeminal neuropathy were 0.9 percent, 0.4 percent, and 0.2 percent, respectively.[5]

SRS has also been used to treat less common skull base tumors such as glomus tumors, craniopharyngiomas, chordomas, and chondrosarcomas. For glomus tumors, two meta-analyses show that local tumor control is greater than 90 percent when used as primary therapy and the risk of injury to cranial nerves IX, X, XI, and XII is approximately 10 percent.[2,27] For craniopharyngiomas, the radiation dose from SRS that can be given is limited by its close proximity to the optic apparatus. The reported local tumor control rate is 85 percent.[28,29] For skull base chordomas, the North American Gamma Knife Consortium conducted a pooled analysis of 71 patients. Local control at five years was 66 percent.[30] Very little data exists on the use of SRS for skull base chondrosarcoma; the reported local control rate ranges from 88 percent to 100 percent.[3,31]

Malignant Primary Tumors and Brain Metastases

Except in a recurrent setting, the role of SRS in the primary management of low-grade glioma is limited.[6] For malignant glioma, a phase III randomized trial by Radiotherapy and Oncology Group (RTOG) showed no benefit to adding SRS to external beam radiotherapy and chemotherapy for glioblastoma.[8] However, it has been used as one of the treatment options for patients with recurrent disease.[8] SRS is mainly used in the setting of recurrent disease after external beam radiotherapy and, to a lesser degree, as a boost after external beam radiotherapy in patients with gross residual disease in the management of ependymoma.[9,10] Overall local tumor rate is approximately 60 percent to 65 percent. However, patients with recurrent disease have a substantial risk of developing neuroaxis dissemination.

Brain metastases are one of the most common indications for SRS. Level I evidence supports its use in the setting of a boost after whole brain radiotherapy (WBRT) in patients with one to three brain metastases.[32] In patients with a single brain metastasis, the addition of SRS to WBRT brings a survival advantage; median survival time increases from 4.9 months to 6.5 months. Patients receiving SRS are more likely to have a stable or improved Karnofsky Performance Status (KPS) score at 6.[32]

Two phase III randomized trials compared SRS to SRS plus WBRT.[33,34] This study from M.D. Anderson Cancer Center showed that, despite a lower incidence of intracranial recurrence in patients receiving SRS plus WBRT, these patients were at greater risk of a significant decline in learning and memory function by four months and their survival was no better compared to patients receiving SRS alone.[33] Multiple studies show that SRS is an effective therapy for patients with recurrent brain metastases.[8] Figure 1 demonstrates a case of a single melanoma brain metastasis treated with Gamma Knife-based SRS with good response.

Benign Disorders

SRS has been used to treat benign conditions, such as AVM, trigeminal neuralgia, and epilepsy. For AVMs, target delineation is accomplished utilizing a combination of angiography and stereotactic magnetic resonance imaging (MRI) or computed tomography. The target volume is the nidus of the AVM. Complete obliteration can take one to three years to occur, and a risk of hemorrhage still exists during this latency period. After complete obliteration of an AVM, this risk is minimal though not eliminated. Whether bleeding rates are unchanged, decreased, or increased after SRS is unclear. The obliteration rate depends on lesion size and radiation dose.[18,35] If the lesion is less than or equal to 3 cm, the overall obliteration rate at three years is 80 percent – much higher than that of lesions greater than 3 cm.[36] A dose-response in terms of obliteration rate has been noted.[19] Doses of 16, 18, and 20 Gy are associated with obliteration rates of approximately 70 percent, 80 percent, and 90 percent, respectively.[19,36] SRS may improve seizure control, with one study reporting a seizure control rate of 51 percent after SRS.[37]

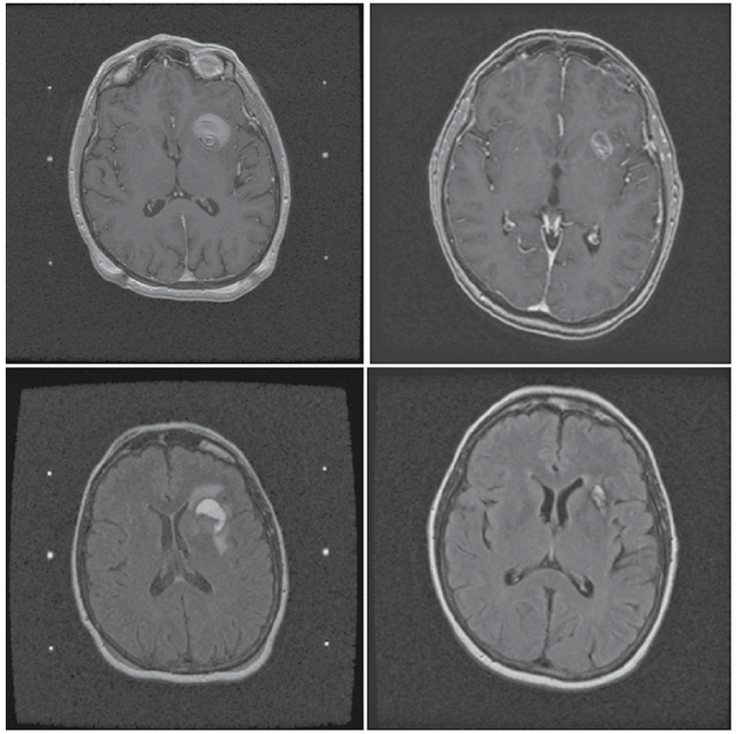

Figure 1. A 58-year-old patient with a large melanoma brain metastasis (left column) received Gamma Knife stereotactic radiosurgery (SRS) to a dose of 18 Gy. Repeat magnetic resonance imaging three months after SRS showed tumor shrinkage and decreased edema (right column). The tumor continued to shrink, and there was no evidence of intracranial recurrence at the time of death (from progressive systemic disease) more than 12 months after SRS.

The risk of complications associated with SRS is determined by location, volume treated, and radiation dose. SRS for AVMs located in high-risk areas, such as the thalamus, basal ganglion, and brainstem, is associated with a higher risk of symptomatic neurologic complications.[38,39] In one of the largest studies, the risk of radiation-induced injury from Gamma Knife-based SRS was 8 percent. The University of Pittsburgh Medical Center developed a system to estimate the risk of radiation injury from SRS for AVMs based on the location and the volume encompassed by the 12 Gy line.[38,39]

Trigeminal neuralgia is defined as sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve. Treatment options include medications, microvascular decompression, radiofrequency rhizotomy, glycerol rhizolysis, balloon compression, and SRS (Gamma Knife or linear accelerator-based). The proximal trigeminal root, typically identified on MRI, is targeted for SRS. The maximum dose had ranged from 70 to 90 Gy; however, based on a study from Mayo Clinic showing a higher risk of trigeminal nerve dysfunction with the use of 90 Gy, the typical dose used now is 80 Gy.[40] Data in the literature show that approximately 75 percent of patients reported complete relief within three months, but this percentage decreased to 50 percent by three years.[41] A lag time of one month after SRS is typically reported. Unfortunately, less than 50 percent of patients were able to permanently stop drug therapy after SRS. Sensory disturbances are the most frequent complications. Patients with recurrent disease may receive a second course of SRS.[42]

Conclusions

SRS has been used to treat various intracranial and skull base tumors and benign conditions with promising outcomes. In situations with multiple treatment options, it is best to review the case in an interdisciplinary conference to determine the best therapy for each patient. Successful treatment is a collaborative effort among radiation oncologists, neurosurgeons, physicists, radiation therapists, and nurses. Interdisciplinary care cannot be overemphasized.

Warren R. Selman, MD, is a consultant for Surgical Theater and IntegraLife, though this relationship has not affected the content of this article. The other authors report no financial relationships relevant to the content of this article.

References

1. Flickinger JC, Kondziolka D, Niranjan A, et al. Acoustic neuroma radiosurgery with marginal tumor doses of 12 to 13 Gy. Int J Radiat Oncol Biol Phys 2004;60:225-230.
2. Guss ZD, Batra S, Limb CJ, et al. Radiosurgery of glomus jugulare tumors: a meta-analysis. Int J Radiat Oncol Biol Phys 2011;81(4):e497-e502.
3. Hasegawa T, Ishii D, Kida Y, et al. Gamma Knife surgery for skull base chordomas and chondrosarcomas. J Neurosurg 2007;107:752-757.
4. Pollock BE, Stafford SL. Results of stereotactic radiosurgery for patients with imaging defined cavernous sinus meningiomas. Int J Radiat Oncol Biol Phys 2005;62:1427-1431.
5. Witt TC. Stereotactic radiosurgery for pituitary tumors. Neurosurg Focus 2003;14:e10.
6. Henderson MA, Fakiris AJ, Timmerman RD, et al. Gamma knife stereotactic radiosurgery for low-grade astrocytomas. Stereotact Funct Neurosurg 2009;87:161-167.
7. Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys 2005;63:37-46.
8. Tsao MN, Mehta MP, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for malignant glioma. Int J Radiat Oncol Biol Phys 2005;63:47-55.

9. Lo SS, Chang EL, Sloan AE. Role of stereotactic radiosurgery and fractionated stereotactic radiotherapy in the management of intracranial ependymoma. Expert Rev Neurother 2006;6:501-507.
10. Lo SS, Abdulrahman R, Desrosiers PM, et al. The role of Gamma Knife Radiosurgery in the management of unresectable gross disease or gross residual disease after surgery in ependymoma. J Neurooncol 2006;79:51-56.
11. Barbaro NM, Quigg M. Epilepsy – radiosurgery for epilepsy. Rev Neurol Dis 2009;6:39.
12. Barbaro NM, Quigg M, Broshek DK, et al. A multicenter, prospective pilot study of gamma knife radiosurgery for mesial temporal lobe epilepsy: seizure response, adverse events, and verbal memory. Ann Neurol 2009;65:167-175.
13. Chang EF, Quigg M, Oh MC, et al. Predictors of efficacy after stereotactic radiosurgery for medial temporal lobe epilepsy. Neurology 2010;74:165-172.
14. House PA, Kim JH, Lanerolle ND, et al. Radiosurgery in epilepsy – pathological considerations. Prog Neurol Surg 2007;20:279-288.
15. Quigg M, Barbaro NM. Stereotactic radiosurgery for treatment of epilepsy. Arch Neurol 2008;65:177-183.
16. Quigg M, Broshek DK, Barbaro NM, et al. Neuropsychological outcomes after Gamma Knife radiosurgery for mesial temporal lobe epilepsy: a prospective multicenter study. Epilepsia 2011;52:909-916.
17. Wegner RE, Oysul K, Pollock BE, et al. A modified radiosurgery-based arteriovenous malformation grading scale and its correlation with outcomes. Int J Radiat Oncol Biol Phys 2011;79:1147-1150.
18. Lunsford LD, Niranjan A, Kondziolka D, et al. Arteriovenous malformation radiosurgery: a twenty year perspective. Clin Neurosurg 2008;55:108-119.
19. Flickinger JC, Kondziolka D, Maitz AH, et al. An analysis of the dose-response for arteriovenous malformation radiosurgery and other factors affecting obliteration. Radiother Oncol 2002;63:347-354.
20. Kondziolka D, Flickinger JC, Lunsford LD, et al. Trigeminal neuralgia radiosurgery: the University of Pittsburgh experience. Stereotact Funct Neurosurg 1996;66 Suppl 1:343-348.
21. Sheehan JP, Williams BJ, Yen CP. Stereotactic radiosurgery for WHO grade I meningiomas. J Neurooncol 2010;99:407-416.
22. Karpinos M, Teh BS, Zeck O, et al. Treatment of acoustic neuroma: stereotactic radiosurgery vs. microsurgery. Int J Radiat Oncol Biol Phys 2002;54:1410-1421.
23. Pollock BE, Lunsford LD, Kondziolka D, et al. Outcome analysis of acoustic neuroma management: a comparison of microsurgery and stereotactic radiosurgery. Neurosurgery 1995;36:215-224; discussion 24-29.
24. Pollock BE. Vestibular schwannoma management: an evidence-based comparison of stereotactic radiosurgery and microsurgical resection. Prog Neurol Surg 2008;21:222-227.
25. Lunsford LD, Niranjan A, Flickinger JC, et al. Radiosurgery of vestibular schwannomas: summary of experience in 829 cases. J Neurosurg 2005;102 Suppl:195-199.
26. Subach BR, Kondziolka D, Lunsford LD, et al. Stereotactic radiosurgery in the management of acoustic neuromas associated with neurofibromatosis Type 2. J Neurosurg 1999;90:815-822.
27. Ivan ME, Sughrue ME, Clark AJ, et al. A meta-analysis of tumor control rates and treatment-related morbidity for patients with glomus jugulare tumors. J Neurosurg 2011;114:1299-1305.
28. Kobayashi T. Long-term results of gamma knife radiosurgery for 100 consecutive cases of craniopharyngioma and a treatment strategy. Prog Neurol Surg 2009;22:63-76.
29. Niranjan A, Kano H, Mathieu D, et al. Radiosurgery for craniopharyngioma. Int J Radiat Oncol Biol Phys 2010;78:64-71.
30. Kano H, Iqbal FO, Sheehan J, et al. Stereotactic radiosurgery for chordoma: a report from the North American Gamma Knife Consortium. Neurosurgery 2011;68:379-389.
31. Krishnan S, Foote RL, Brown PD, et al. Radiosurgery for cranial base chordomas and chondrosarcomas. Neurosurgery 2005;56:777-784.
32. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004;363:1665-1672.
33. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009;10:1037-1044.
34. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295:2483-2491.
35. Lunsford LD, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for arteriovenous malformations of the brain. J Neurosurg 1991;75:512-524.
36. Pollock BE, Meyer FB. Radiosurgery for arteriovenous malformations. J Neurosurg 2004;101:390-392.
37. Schauble B, Cascino GD, Pollock BE, et al. Seizure outcomes after stereotactic radiosurgery for cerebral arteriovenous malformations. Neurology 2004;63:683-637.
38. Flickinger JC, Kondziolka D, Maitz AH, et al. Analysis of neurological sequelae from radiosurgery of arteriovenous malformations: how location affects outcome. Int J Radiat Oncol Biol Phys 1998;40:273-278.
39. Flickinger JC, Kondziolka D, Lunsford LD, et al. Development of a model to predict permanent symptomatic postradiosurgery injury for arteriovenous malformation patients. Arteriovenous Malformation Radiosurgery Study Group. Int J Radiat Oncol Biol Phys 2000;46:1143-1148.
40. Pollock BE, Phuong LK, Foote RL, et al. High-dose trigeminal neuralgia radiosurgery associated with increased risk of trigeminal nerve dysfunction. Neurosurgery 2001;49:58-62.
41. Lopez BC, Hamlyn PJ, Zakrzewska JM. Stereotactic radiosurgery for primary trigeminal neuralgia: state of the evidence and recommendations for future reports. J Neurol Neurosurg Psychiatry 2004;75:1019-1024.
42. Park KJ, Kondziolka D, Berkowitz O, et al. Repeat Gamma Knife Radiosurgery for Trigeminal Neuralgia. Neurosurgery 2011 Aug 1 [Epub ahead of print].

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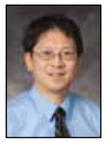

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Glioblastoma Multiforme Clinical Trial Studies 5-Aminolevulinic Acid for Fluorescence-Guided Resection

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Introduction

Glioblastoma multiforme (GBM) is a devastating diagnosis, with a median survival of less than one year and less than 5 percent two-year survival.[1] The past three decades have shown few advances in treatment. Several recent studies have demonstrated a clear link between completeness of tumor resection of malignant brain, quality of life, and survival.[2-7] In attempting full resection, neurosurgeons often find it challenging to locate the margin of a tumor.

Case 1305: Fluorescence-Guided Resection

Clinical trials utilizing intravenously administered fluorescing brain tumor photosensitizers, referred to as porphyrins, began at Roswell Park Cancer Center in Buffalo, N.Y.[8] Initially, the goal of these studies was not simply defining the border of the tumor but rather inducing cell death with photodynamic therapy (PDT). PDT is the activation of tumor-localized drugs by light of a wavelength absorbed by the drug and the resultant generation of tissue-damaging reactive-oxygen species.[9] Fluorescence-guided resection (FGR) is the activation of often the same tumor-localized drug by a second wavelength and the resultant emission of fluorescent light.[5] While the photosensitizers that were initially studied proved ineffective therapeutically for tumor necrosis or localization as an aid in resection, porphyrin-based FGR has been shown to lengthen progression-free survival following brain tumor resection in the past decade.

Clinical Application of FGR

Currently, the most effective agent to have received regulatory approval is 5-Aminolevulinic Acid (5-ALA), which is metabolically converted to Protoporphyrin IX (PpIX). PpIX preferentially accumulates in tumor over normal brain. When exposed to 400 nm (blue) light during resection, the tumor glows pink. With a specially modified surgical microscope equipped with 405 nm light emission and filters to capture and display the expected pink fluorescence, the surgeon can detect and use fluorescence to locate the tumor and guide resection.

Most of the porphyrin-like photosensitizers pass through the blood stream to accumulate in metabolically active tissues, such as retina, gut, blood vessel, skin, lesion, or tumor. Some photosensitizers will clear from the blood stream quickly and preferentially accumulate in tumor rather than non-tumor tissue. 5-ALA is then metabolized into PpIX, and it is PpIX that preferentially accumulates in GBM and allows FGR.

In a randomized phase III clinical trial in Germany undertaken by Stummer and colleagues, surgeons were able to achieve a complete resection (i.e., no unintended residual tumor was observed in post-resection magnetic resonance imaging [MRI]) in 65 percent of patients using 5-ALA versus only 36 percent of untreated patients.[5] As had been predicted, the more complete resection seen in the PpIX-FGR group correlated with an increase in progression-free survival.[2-7] Stummer and colleagues found that six-month survival in the 5-ALA group was 41.5 percent (range 32.8–49.2) versus 21.1 percent (range 14.0–28.2) in the control group, a difference of 19.9 percent (range 9.1–30.7).[5] However, computer-aided navigational (stereotactic) techniques, such as those routinely employed at UH Case Medical Center and elsewhere in the United States, were not employed in the phase III clinical trial. There was no difference in the frequency of adverse events between the two groups.

Stummer and colleagues' 5-ALA-FGR protocol is now approved as standard of care by the European Union's equivalent of the Food and Drug Administration (FDA), the European Medicines Agency.[5] However, the FDA has not approved 5-ALA for use in the brain; thus, the agent can only be utilized for a specific scientific trial. Dr. Sloan and colleagues have recently received FDA approval to perform additional studies with this agent in combination with computer-aided navigational techniques and intraoperative MRI. A study of the efficacy of PpIX-FGR is also ongoing at Dartmouth University.[10]

Goals of Case 1305

The Brain Tumor & Clinical Neuro-Oncology Center at UH Case Medical Center is sponsoring a study, CASE 1305 "Fluorescence-Guided Detection of Malignant Gliomas," that is currently attempting to more precisely quantitate 5-ALA derived fluorescence by comparing the surgeon's assessment of intraoperative PpIX fluorescence, the diagnosis of resected tumor, and the actual uptake of PpIX in resected tissue using an optical imaging device that may be more sensitive than the surgeon's eye.[11] The work by Stummer and colleagues refers to "solid" and "vague" fluorescence.[12] However, utilizing a digital probe, in collaboration with colleagues at the University of Toronto, we can accurately measure PpIX concentration at any location that appears to be fluorescing. Our goal is to determine the relationship between drug dose, time since administration, objective fluorescence, and tumor histology.

We hypothesize that the use of qualitative fluorescence assessment will facilitate improved tumor resection efficacy and progression-free patient survival. We will compare residual tumor detection by in vivo qualitative and quantitative fluorescence imaging of the biopsied tissue as a gold standard. The secondary objective of this study is to assess the correlation between the recorded in vivo qualitative assessment of fluorescence signal from the neurosurgeon with the absolute PpIX concentration detected intraoperatively and in ex-vivo tissue biopsy specimens. Finally, a tertiary objective of this study is to determine the association between the presence of fluorescence in the surgical cavity and the postoperative image enhancement seen on MRI (Figure 1). This association includes the relationship between the amount and location of residual tumor detected by fluorescence, PpIX concentration, and intraoperative frameless stereotaxy following maximal resection versus residual tumor located postoperatively in radiological images.

Conclusion

5-ALA-mediated FGR may lead to safer, more effective ways of maximizing resection efficacy and progression-free survival in patients with brain tumors. In addition, more sensitive and quantitative methodologies for the detection and measurement of PpIX fluorescence may lead to wider adoption of this procedure in the United States and possibly to its approval by the FDA.

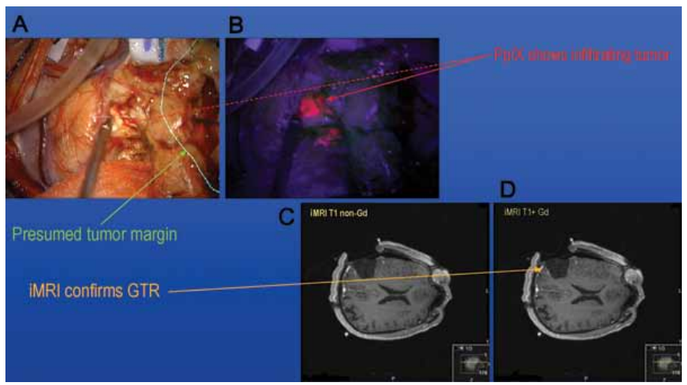

Figure 1: (A) View through surgeon's microscope showing outline of the tumor margin as it appeared on the preoperative magnetic resonance imaging. It appears that a gross total resection (GTR) has been achieved. (B) However, under blue light (Zeiss Blue 400™ [Carl Zeiss International, Jena, Germany]) there is obvious pink fluorescence just outside the presumed tumor margin. Biopsy confirmed the presence of viable tumor, which was resected. Intraoperative magnetic resonance imaging (iMRI) after resection of this area (C) without and (D) with Gadolinium (Gd) contrast demonstrates that no residual tumor remains.

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References

1. Barnholtz-Sloan JS, Sloan AE, Schwartz AG. Chapter 25: Cancer of the Brain and Other Central Nervous System. 2007. Available at: http://seer.cancer.gov/publications/survival/surv_brain.pdf. CBTRUS: http://www.cbtrus.org/2009EighteenStates/CBTRUSReport-2002-2006.pdf. Accessed October 1, 2011.
2. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extend of resection and survival. J Neurosurg 2001;95(2):190-198.
3. Keles GE, Lamborn KR, Berger MS. Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. J Neurosurg 2001;95(5):735-745.
4. Laws ER, Parney IF, Huang W, et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. J Neurosurg 2003;99(3):467-473.
5. Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 2006;7(5):392-401.
6. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery 2008;62(4):753-764; discussion 264-266.
7. Sanai N, Berger MS. Operative techniques for gliomas and the value of extent of resection. Neurotherapeutics 2009;6(3):478-486.
8. Dougherty TJ. Use of hematoporphyrin in photodynamic therapy. J Photochem Photobiol B 1991 Mar;8(4):439.
9. Stylli SS, Kaye AH, MacGregor L, et al. Photodynamic therapy of high grade glioma – long-term survival. J Clin Neurosci 2005;12:389-398
10. Valdés PA, Kim A, Brantsch M, et al. δ-aminolevulinic acid-induced protoporphyrin IX concentration correlates with histopathologic markers of malignancy in human gliomas: the need for quantitative fluorescence-guided resection to identify regions of increasing malignancy. Neuro Oncol 2011;13(8):846-856.
11. Valdés PA, Leblond F, Kim A, et al. Quantitative fluorescence in intracranial tumor: implications for ALA-induced PpIX as an intraoperative biomarker. J Neurosurg 2011;115(1):11-17.
12. Stummer W, Novotny A, Stepp H, et al. Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients. J Neurosurg 2000;93(6):1003-1013.

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New Neurological Applications for Botulinum Toxin

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Botulinum Toxin

Botulinum toxin is a protein derived from the bacterium *Clostridium botulinum*. It irreversibly binds to the presynaptic receptor, is endocytosed, and then blocks acetylcholine release. Botulinum toxin generally exerts its clinical effects within one week and loses its benefit after approximately three months. To minimize the rare incidence of antibody formation against botulinum toxin, it is not injected more often than once every three months.

There are two major subtypes of botulinum toxin: type A and type B. For many years, there was one botulinum toxin type A product, onabotulinumtoxinA (Botox, Allergan, Inc.), and one botulinum toxin type B product, rimabotulinumtoxinB (Myobloc, Solstice Neurosciences, LLC). More recently, two new subtypes of type A botulinum toxin have been approved by the U.S. Food and Drug Administration (FDA), namely incobotulinumtoxinA (Xeomin, Merz Pharmaceuticals, LLC) and abobotulinumtoxinA (Dysport, Tercica, Inc. a subsidiary of the Ipsen Group).[1]

Although first developed in the 1960s and studied in human subjects in 1977 for treatment of strabismus, botulinum toxin is now used to treat a myriad of neurological and non-neurological conditions.[2] For movement disorders, neurologists typically utilize botulinum toxin to treat dystonia, including spasmodic torticollis (involving the neck), focal dystonia (involving the extremities), orofacial dystonia (involving the jaw and face), and blepharospasm (involving the eyes). Other common applications for botulinum toxin in a movement disorders practice include hemifacial spasm and sialorrhea (hypersalivation). Non-neurologists utilize botulinum toxin for cosmetic and urinary indications as well as to treat spasmodic dysphonia (vocal dystonia). In this article, we summarize the use of onabotulinumtoxinA for the recently FDA-approved indications of chronic migraine headache and upper limb spasticity.

Chronic Migraine Headache

Chronic daily headache of long duration has been defined as a primary headache that occurs for at least four hours per day, at least 15 days per month, over a duration of greater than three months.[3] Chronic migraine headache is one particular subtype of chronic daily headache that can cause substantial disability, with reduced productivity at home and at work, for a majority of patients.[4]

Chronic migraine headache is defined as headache for at least 15 days per month in a patient with a diagnosis of migraine and without medication overuse. Specifically, according to 2006 International Classification of Headache Disorders (ICHD)-2 criteria, chronic migraine headache is a migraine or tension-type chronic daily headache with a history of five prior attacks meeting diagnostic criteria for migraine without medication overuse.[5] Furthermore, migraine must occur more than eight days per month for greater than three months, and the patient must have either of the following two characteristics:

- Either nausea or vomiting, or photophobia and phonophobia, plus two of the following four criteria:
  - Unilateral pain
  - Pulsating pain
  - Moderate to severe intensity
  - Exacerbated by, or avoiding, exertion
- Relief by triptan or ergot.[5]

Chronic migraine headache, which by definition excludes medication overuse headache, is often first treated with prophylactic medications, such as tricyclic antidepressants, anticonvulsants (topiramate and valproate), and beta blockers (propranolol). OnabotulinumtoxinA (Botox, Allergan, Inc.) has been studied for a number of years.

Botulinum Toxin Type A for Chronic Migraine Headache

In two head-to-head studies, onabotulinumtoxinA and topiramate showed similar efficacy.[6,7] The first study showed reduced adverse effects and fewer dropouts in the botulinum toxin-treated group, whereas the second study found a similar rate of dropouts and adverse effects, with the exception of a higher rate of nausea in the botulinum toxin-treated group compared to topiramate (59.1 percent vs. 27.3 percent of subjects, respectively).[6,7]

Two large clinical studies conducted from 2006 to 2008 investigated the efficacy and safety of onabotulinumtoxinA injected every 12 weeks for treatment of chronic migraine headache.[8] The first of these studies was Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1, a phase III double-blind, placebo-controlled, 24-week study, with a 32-week open-label extension that enrolled 679 subjects.[9] This study did not achieve its primary endpoint of reduced headache episodes but did achieve significant results for secondary endpoints (headache days, migraine days, and within-group improvement from baseline).[9] There were no treatment-related serious adverse events (AEs), and only 4.1 percent of treated subjects discontinued the study due to AEs (compared to 0.9 percent of placebo-treated subjects).[9]

The PREEMPT 2 study was also a phase III double-blind, placebo-controlled, 24-week study, with a 32-week open-label extension that enrolled 705 subjects.[10] The primary endpoint, mean change in headache episodes per 28 days, showed significantly greater reduction in the onabotulinumtoxinA-treated group (-9.0) despite a robust placebo effect (-6.7). Secondary endpoints were also achieved.[10] Ptosis, muscle pain, and stiffness were more frequent in the treated group, and there was one treatment-related serious AE (hospitalization for migraine); only 3.5 percent of treated subjects discontinued the study due to AEs (compared to 1.4 percent of placebo-treated subjects).[10]

A pooling of the results of these two similarly designed studies achieved its primary outcome (headache frequency) as well as its secondary outcomes.[8] Another paper described a pooled analysis in which impact of headache as measured by Headache Impact Test-6 and quality of life as measured by Migraine-Specific Quality of Life Questionnaire v2.1 improved with botulinum toxin treatment compared to placebo.[11]

The manufacturer recommends a treatment approach, extrapolated from these large clinical studies, that involves five units injected in each of four sites in the frontalis muscle, two injection sites in the corregator, one in the procerus, six in the occipitalis, eight in the temporalis, six in the trapezius, and four in the cervical paraspinal muscles, for a total dose of 155 units.[12] Injections are typically repeated about every three months, similar to many other botulinum toxin indications.

Upper Limb Spasticity

Spasticity is a velocity-dependent increase in muscle tone and resistance that is common in a myriad of neurological conditions, including stroke, multiple sclerosis, and amyotrophic lateral sclerosis. Spasticity also affects many patients with cerebral palsy, some of whom are already receiving botulinum toxin for dystonic posturing. With time, a velocity-independent spastic posture can develop, causing significant disability, limiting range of motion, and sometimes interfering with hygiene. Furthermore, untreated spasticity can lead to contractures and greater loss of upper extremity function.

Treatment options for upper extremity spasticity include physical and occupational therapy and muscle relaxant medications, such as baclofen, clonazepam, and tizanadine. Intrathecal baclofen pumps are sometimes implanted when oral baclofen causes insufficient benefit or is limited by adverse effects. However, all of the oral medications have potential to cause adverse central nervous system effects such as fatigue, and intrathecal baclofen pumps introduce risks such as infection or pump failure.

Botulinum Toxin Type A for Upper Limb Spasticity

The goal of botulinum toxin injection is to reduce the severity of upper limb spasticity, improve the patient's functional status, and prevent the incidence of contractures. Botulinum toxin is injected into the affected muscles as suggested by physical examination, electromyography (EMG), and discussion with the patient of which muscle groups have bothersome spasticity that impair quality of life. Therefore, the pattern of injection is tailored to the specific patient. Botulinum toxin injection can be repeated approximately every three months. EMG guidance is used for these injections (Figure 1).

In 1996, Simpson and colleagues studied the use of onabotulinumtoxinA to treat upper limb spasticity due to stroke in a randomized, double-blind, placebo-controlled study of standardized regimens of low, medium, and high doses of onabotulinumtoxinA injected into the biceps and the flexor carpi radialis and flexor carpi ulnaris muscles of 37 subjects.[13] There was a significant reduction in upper extremity spasticity in the treated groups, with no treatment-related serious AEs.[13]

A subsequent randomized, double-blind, placebo-controlled study investigating a single dose of onabotulinumtoxinA versus placebo for treatment of post-stroke wrist and finger spasticity in 126 subjects found significant improvement in flexor tone and Disability Assessment Scale Score in the treated group relative to placebo, with 6 percent of onabotulinumtoxinA-treated subjects experiencing weakness but no major AEs.[14] In contrast, another randomized, double-blind, placebo-controlled study of various onabotulinumtoxinA doses in 91 subjects with post-stroke spasticity found a dose-dependent decrease in muscle tone but no improvement in disability or quality of life.[15]

The Botulinum Toxin for the Upper Limb after Stroke (BoTULS) study, a randomized controlled trial (RCT) of abobotulinumtoxinA and upper limb therapy versus therapy alone for post-stroke spasticity in 333 subjects, showed improvement in some upper limb basic functional activities and upper limb pain, although there was no significant improvement in upper limb function (the primary outcome measure) relative to the therapy-treated group.[16] Incidence of flu-like symptoms and malaise was higher in the treated group, and one subject developed dysphagia that was potentially treatment-related.[16]

Bakheit and colleagues produced significant improvement in muscle tone but not functional disability in 82 subjects with post-stroke spasticity that were randomized to abobotulinumtoxinA at three different doses versus placebo.[17] Fifty-nine post-stroke spasticity subjects in another RCT showed improvement in passive range of movement at the elbow and global assessment of benefit that was still present at 16 weeks after injection in the abobotulinumtoxinA-treated group relative to placebo.[18] Similarly, abobotulinumtoxinA caused an improvement in passive range of motion that was dose-related when used to treat upper limb spasticity in 21 subjects with stroke and head injury, but increasing the total dose did not increase the duration of the clinical effect.[19]

In contrast, disability, caregiver burden, and forearm spasticity were significantly improved for up to 12 weeks (whereas elbow spasticity and pain were not improved) in a randomized, double-blind, placebo-controlled study of abobotulinumtoxinA in 40 subjects with post-stroke spasticity and a functionally useless arm.[20]

Figure 1: Botulinum toxin for upper limb spasticity from C1-C2 cervical spine fracture and resultant anoxic brain injury (Photograph courtesy of Christina Whitney, PhD).

Conclusions

Botulinum toxin has been utilized by neurologists for decades to treat a host of neurological conditions. The indications recently approved by the FDA for onabotulinumtoxinA, namely the treatment of chronic migraine headache and upper limb spasticity, will broaden the tools that are available to neurologists in managing these conditions.

The large clinical studies of onabotulinumtoxinA in treating chronic migraine headache demonstrated efficacy and safety of this treatment. OnabotulinumtoxinA is a useful prophylactic agent in patients who have failed oral agents or who would not be expected to tolerate oral agents. It is expected to reduce the rate of hospitalization and emergency room visits in this patient population.

Upper limb spasticity is a major problem for patients with a number of different underlying neurological conditions and can strongly impact quality of life. The existing therapies are often limited by adverse effects, such as fatigue, and by unwillingness to absorb the risks of a baclofen pump. OnabotulinumtoxinA is an additional treatment option that is now available to patients with spasticity. Studies suggest that patient selection is important, in that patients who will gain some functional or quality-of-life benefit, such as improved hand utility, decreased pain, or better hygiene, may be expected to benefit most from the injections.

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References

1. Benecke R, Jost WH, Kanovsky P, et al. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. Neurology 2005;64(11):1949-1951.
2. Truong D, Dressler D, Hallett M. Botulinum toxin: history of clinical development. In: Truong D, Dressler D, Hallett M, eds. Botulinum Toxin Therapy. New York: Cambridge University Press, 2009:9.
3. Bigal ME, Lipton RB. The differential diagnosis of chronic daily headaches: an algorithm-based approach. J Headache Pain 2007;8(5):263-272.
4. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. Neurology 2008;71(8):559-566.
5. Manack A, Turkel C, Silberstein S. The evolution of chronic migraine: classification and nomenclature. Headache 2009;49(8):1206-1213.
6. Cady RK, Schreiber CP, Porter JA, et al. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache;51(1):21-32.
7. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache 2009;49(10):1466-1478.
8. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache;50(6):921-936.
9. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 2010;30(7):793-803.
10. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 2010;30(7):804-814.
11. Lipton RB, Varon SF, Grosberg B, et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. Neurology;77(15):1465-1472.
12. Allergan. Highlights of Prescribing Information (OnabotulinumtoxinA Product Insert). In. Irvine, CA; 2010.
13. Simpson DM, Alexander DN, O'Brien CF, et al. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. Neurology 1996;46(5):1306-1310.
14. Brashear A, Gordon MF, Elovic E, et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. N Engl J Med 2002;347(6):395-400.
15. Childers MK, Brashear A, Jozefczyk P, et al. Dose-dependent response to intramuscular botulinum toxin type A for upper-limb spasticity in patients after a stroke. Arch Phys Med Rehabil 2004;85(7):1063-1069.
16. Shaw LC, Price CI, van Wijck FM, et al. Botulinum Toxin for the Upper Limb after Stroke (BoTULS) Trial: effect on impairment, activity limitation, and pain. Stroke;42(5):1371-1379.
17. Bakheit AM, Thilmann AF, Ward AB, et al. A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke. Stroke 2000;31(10):2402-2406.
18. Bakheit AM, Pittock S, Moore AP, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke. Eur J Neurol 2001;8(6):559-565.
19. Smith SJ, Ellis E, White S, Moore AP. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. Clin Rehabil 2000;14(1):5-13.
20. Bhakta BB, Cozens JA, Chamberlain MA, Bamford JM. Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. J Neurol Neurosurg Psychiatry 2000;69(2):217-221.

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