Trending Topics in Neuro-Ophthalmic Disease

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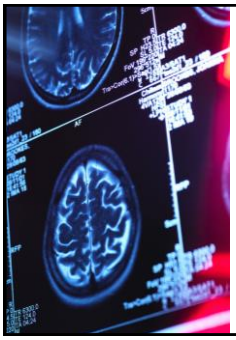

Today's Topics

Chronic Intracranial Hypertension
Arteritic AION
Demyelinating Optic Neuropathies
Myasthenia Gravis
MS Treatment Update

Idiopathic Intracranial Hypertension

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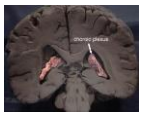
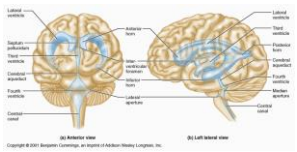
Updates Include Two Key Areas:

- Etiology/pathophysiology
- Treatment/management

CSF Production

CSF is produced by the choroid plexus of the ventricular system and flows through the interventricular foramina into the third ventricle then through the cerebral aqueduct into the fourth ventricle and into the subarachnoid space.



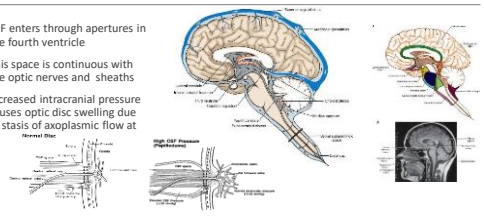


The Subarachnoid Space

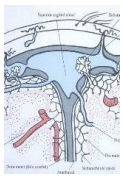
CSF enters through apertures in the fourth ventricle

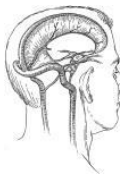
This space is continuous with the optic nerves and sheaths

Increased intracranial pressure causes optic disc swelling due to stasis of axoplasmic flow at th



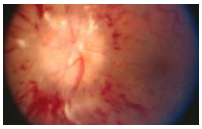
CSF Absorption

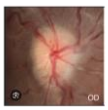




The chief route of absorption of CSF in the brain is **passively,** through the arachnoid granulations that protrude into the venous sinuses and diploic veins. These vessels drain into the jugular vein.

Key Opthalmic Finding is Papilledema





Papilledema

- Optic nerve swelling due to raised intracranial pressure

Acute vs chronic

- Acute presentations have more sinister etiologies
  - Intracranial structural lesions, meningitis, severe hypertension, subarachnoid hemorrage
- Chronic presentations have more benign etiologies
  - Systemic diseases, medications, obesity
  - Pseudotumor Cerebri

Most cases of chronic papilledema involve impaired reabsorption, due to subtle changes in blood viscosity, cellular characteristics of involved tissues, or an altered pressure gradient within the venous sinuses

REABSORPTION PROBLEMS LEAD TO INCREASED INTRACRANIAL PRESSURE

MEDICATIONS, SYSTEMIC DISORDERS, NUTRITIONAL FACTORS, OBESITY HAVE ALL BEEN ASSOCIATED

Diagnostic Algorithm for Papilledema

Rule out a structural cause	Magnetic resonance imaging (MRI)
Identify the underlying cause	Careful history is crucial to the identification of contributing systemic disorders, medications and/or supplements! Magnetic resonance venogram (MRV) Blood work
"Idiopathic" PTC **syndrome is a diagnosis of exclusion!**	

Clarifying the Obesity Factor

When systemic disease, medications or other factors are ruled out, we have used "idiopathic" in lieu of pseudotumor cerebri" to describe the remainder of the patients

"Idiopathic" patients tend to be obese females in their childbearing years

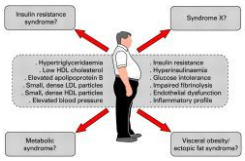
We used this term because we did not understand the underlying pathophysiology.	We are learning more about pathophysiologic mechanisms related to obesity

Pathophysiologic Theories For Obesity Related PTC

Mechanical Factors	• May disrupt the pressure gradient involved in venous reabsorption
Endocrine Factors	• May have an impact on CSF reabsorption due to outflow resistance caused by effects on epithelial cells
Cellular Factors	• May affect CSF reabsorption via inflammatory changes resulting in microthrombosis

Mechanical Factors and Obesity

Obesity raises intraabdominal pressure which could impair venous drainage
- Sugarman et al. Neurology, 1997
- This does not explain the female predominance



Endocrine Factors and Obesity

Adipose is an actively secreting endocrine tissue
- Adipose is an active secretor of estrogen (Hetemaki et al, 2021)
- Obese females have higher levels of CSF leptin, estradiol and testosterone (Abdelghaffar et al, 2022)

Androgen Secretion
- Obese women with IIH have a distinct androgen excess profile which can modulate CSF absorption (O'Reilly et al, 2019)
- Women with Polycystic Ovarian Syndrome (PCOS) have a four-fold increase in incidence in PTC and have the same unique androgen excess profile
- Case reports have described the incidence of IIH in female to male sex reassignment (Klein et al, 2013)

Sex Predilection and PTC
- Gynecoid obesity is more commonly associated with PTC than abdominal obesity (Kesler 2009)
- Sex hormones are implicated due to absence of a gender preference before puberty (Kesler 2010)

Cellular Factors and Obesity Related PTC

Obesity is associated with chronic inflammation which can lead to a prothrombic state (Sinclair et all 2008)
- Obese females have higher levels of CSF leptin, estradiol and testosterone (Abdelghaffar et al, 2022)
- Numerous studies point to increased expression of cytokines (leptin), adipokines, interleukins, macrophage chemotactic protin-1.

Idiopathic Intracranial Hypertension is Not Really Idiopathic!!

Pseudotumor Cerebri Syndrome

Obesity Related PTC

Managing PTC Syndrome

Address the Disease	• Identify and remove/manage the causative agent
Manage Comorbidities	• Headache • Vision loss

Weight loss is the only remedy that addresses the cause in obesity related cases

But how much is enough to have a significant impact on ICP?

15% reduction has been shown to be effective in most
- Sinclair et al, 2010

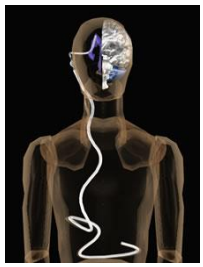
As little as 3.5% weight reduction is effective in many
- Skau et al, 2011

Weight Loss Options

Lifestyle
- Weightwatchers, itrackbites
- Dieticians/nutritionists

Medications

Bariatric Surgery
- Gastric bypass
- Sleeve/banding

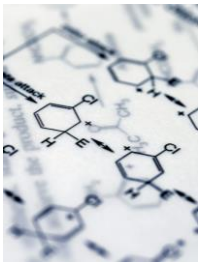


ICP should be addressed more aggressively when there is vision loss or headache

Medications

Surgical
- Shunting
- Optic Nerve Sheath Fenestration
- Venous stenting

There are no controlled studies to validate benefits



Acetazolamide

Carbonic anhydrase inhibitor
- Decreases CSF production

500-4,000 mg/day

Poorly tolerated in most
- Polyuria, lightheadedness, drowsiness, nausea, dysgeusia, paresthesia, diarrhea, fatigue
- Less than 50% adherence to treatment

Diuretic agents have also been utilized

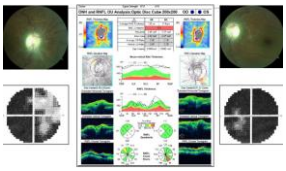
ARTICLE

Update on the Surgical Management of Idiopathic Intracranial Hypertension

Mukherjee, Nisha ; Bhatti, M. Tariq

Current neurology and neuroscience reports, 2014, Vol.14 (3), p.438-438

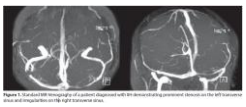
Surgical treatment of IIH is reserved for patients who
- Cannot tolerate medical therapy
- Are nonadherent to medical therapy,
- Develop progressive symptoms despite maximal medical therapy or
- Present with fulminant visual loss.



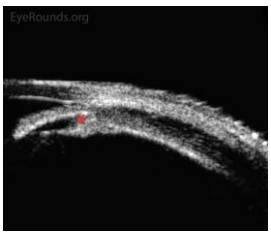
Venous Stenting

Based on the hypothesis that there is venous stenosis of the transverse sinus

Controversial; unclear whether venous stenosis is a cause or effect of ICP increase
- One study showed long-term benefit on ICP (Ahmed et al, 2011)
- No controlled studies to support
- Consensus is that flow disturbances in the transverse sinus are an effect of high ICP rather than a cause (McGeeney BE, 2016)



An update on the pathophysiology of idiopathic intracranial hypertension (Idio pseudotumor cerebri



Managing Headaches

Topiramate

Migraine may be a comorbidity
- Persistance after ICP lowering (Ekizoglu E et al, 2012)
- 68% of IIH patients have migraine phenotype (Friedman et al, 2017)

Side Effects
- Brain fog, drowsiness, altered taste, clumsiness
- Angle closure secondary to choroidal effusion!

Adherence may be less than 50%
- Linde et al 2013

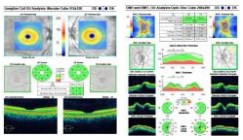
Our Treatment Approach to Obesity Related PTC

PAPILLEDEMA WITHOUT VISUAL COMPROMISE

PAPILLEDEMA WITH VISUAL COMPROMISE

PAPILLEDEMA WITH HEADACHES

Papilledema without visual compromise



Conservative approach

Weight loss

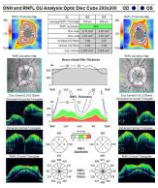
Visual fields and OCT are key studies!!

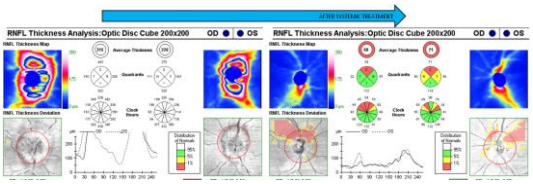
OCT in Papilledema

Details the extent/severity of disc edema

Monitoring response to treatment

Early detection of nerve damage
- Early NFL damage can be masked by the NFL edema
- The ganglion cell layer is useful in getting a better perspective of early damage





Response to Treatment

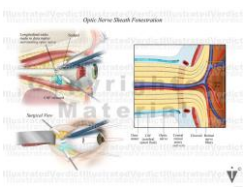
Papilledema with Visual Compromise

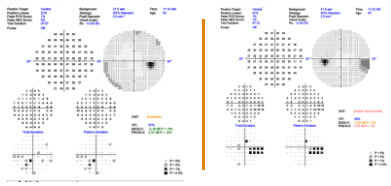
Visual Fields and OCT are indicators of functional and structural integrity of the optic nerve

ICP must be lowered

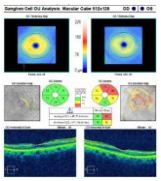
Acetazolamide
- Dose depends on presentation

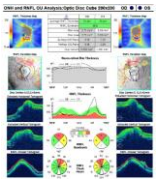
Optic nerve sheath fenestration
- No impact on ICP
- No controlled studies but reports show potential to improve visual function and prevent further loss
- Mechanism is not well understood





Middle Aged Female With IIH





Imaging (GCA) Shows Early Compromise

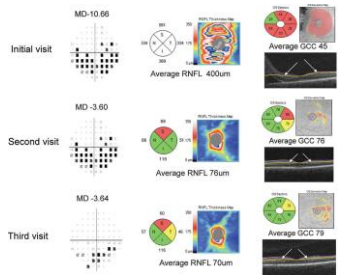
Update: Ganglion cell analysis is a potential indicator of early neuronal loss

Ganglion Cell Complex Analysis as a Potential Indicator of Early Neuronal Loss in Idiopathic Intracranial Hypertension

Geetha Athappilly, Ignacio García-Basterra, Flavia Machado-Miller, Thomas R. Hedges, Carlos Mendoza-Santiesteban & Laurel Vuong

To cite this article: Geetha Athappilly, Ignacio García-Basterra, Flavia Machado-Miller, Thomas R. Hedges, Carlos Mendoza-Santiesteban & Laurel Vuong (2019) Ganglion Cell Complex Analysis as a Potential Indicator of Early Neuronal Loss in Idiopathic Intracranial Hypertension, Neuro-Ophthalmology, 43:1, 10-17, DOI: 10.1080/01658107.2018.1476558

GCC integrity also very useful when the visual fields are unreliable



Papilledema with Headaches

Topiramate
- Three benefits
  - Addresses headache
  - Mild inhibition of carbonic anhydrase
  - Suppresses appetite
- Teratogenic
- Side effects

Diamox will also relieve headaches by lowering ICP, provided the headaches are not migraine

When can medication be stopped?

No clear answer

We wait for a 5-10% reduction in weight

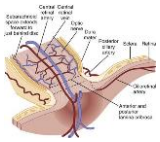
Meds are tapered

Response is monitored with OCT
- OCT is also key in the evaluation of the structural integrity of the optic nerves

Arteritic AION

Anterior Ischemic Optic Neuropathy

Anterior ischemic optic neuropathy (AION) is an ischemic, non-inflammatory condition involving the anterior and retrolaminar portions of the optic nerve



Pathogenesis

AION results from hypoperfusion of the short posterior ciliary arterial branches that supply the anterior optic nerve

- Small vessel atherosclerotic disease combined with low perfusion pressure
- Inflammatory vasculitis of the posterior ciliary or more proximal arteries

This results in infarct of the territory supplied by the posterior ciliary arteries. The infarction can be focal or widespread, depending on the degree of hypoperfusion

Risk Factors for AION

Hypertension

Diabetes

Atherosclerosis

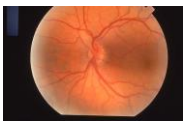
Small optic nerves

Inflammatory vasculitis**

- For the arteritic form only

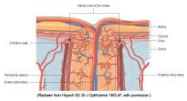
A combination of mechanical and atherosclerotic factors, combined with hypoperfusion, contributes to the process. Physiologic factors may also play a role.

**Factors related to inflammatory vasculitis will be discussed as a separate category



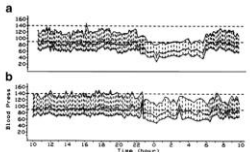
Non-arteritic AION

Non-arteritic AION is typically noticed upon awakening. Nocturnal reductions in blood pressure combined with small vessel atherosclerotic disease are thought to play an important role in pathogenesis. Hypertensive patients who take their medication in the evening are at particular risk for significant nocturnal BP reductions



Nocturnal Hypoperfusion

Fig. 3 Twenty-four-hour ambulatory blood pressure recording in a patient taking Verapamil (a calcium channel blocker). a When on 160 mg morning and bedtime and 80 mg at noon, during sleep systolic blood pressure dropped from 135 mmHg to 80 mmHg and diastolic from 70 mmHg to about 35 mmHg. b On stopping the bedtime dose, nocturnal hypotension improved markedly



Non-arteritic anterior ischemic optic neuropathy versus cerebral ischemic stroke

Sohan Singh Hayreh

Additional Risk Factors

Surgery

- Hypotensive factors

Sleep Apnea

- Hypoxia
- Altered autoregulation
- Elevated ICP during apneic spells may contribute to optic nerve damage

Obstructive Sleep Apnea and Nonarteritic Anterior Ischemic Optic Neuropathy: Evidence for an Association

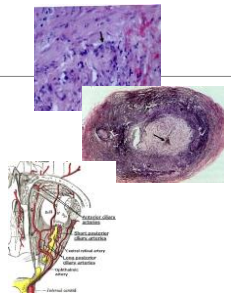
Arteritic AION

AION that occurs in the setting of giant cell (temporal) arteritis

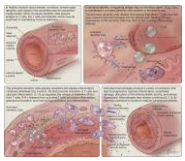
Predilection for GST, vertebral, **ophthalmic** and **posterior ciliary** arteries

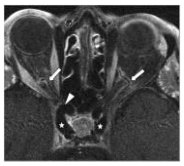
Branches of ophthalmic and posterior ciliary become occluded, resulting in hypoperfusion of more distal arteries supplying the anterior optic nerve

THE MECHANISM OF THE HYPOPERFUSION IS VASCULITIC OCCLUSION OF THE MORE PROXIMAL VASCULATURE



Pathophysiology





Diagnosis of Arteritic AION

Clinical Features
- Signs
- Symptoms

Serologic Testing

Vascular Features
- IVFA
- OCTA
- Ultrasonic

Pathologic Features

American College of Rheumatology Criteria
- Age > 50 years
- New Headache
- TA abnormality (tenderness, or decreased pulsation)
- Elevated ESR
- Abnormal TA biopsy

Presence of any 3 yields a sensitivity of 93.5% and specificity of 91.2%

Arteritic Symptoms

Scalp tenderness

Jaw claudication

Mild fever

Arthralgias; myalgias

Malaise

Which arteritic sx has the highest predictive value for a positive temporal artery biopsy?

Scalp tenderness

Jaw claudication

Arthralgias and myalgias

Fever/malaise

Hayreh et al.

363 patients with AION; (+) TA biopsy in 106

Odds of a positive TA biopsy:	
Jaw claudication	9x
Neck pain	3.4x
CRP > 2.45	3.2x
ESR >47	2x
Age 75+	2x

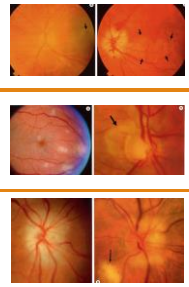
Successive Presentation of Arteritic and Non-arteritic Anterior Ischemic Optic Neuropathy

Matthew Benage MD, Anthony T. Chung MD, Randy H. Kardon MD, PhD

Posted July 23, 2018

Characteristic	AAION	NAION
Age	Mean: 70 yrs	Mean: 60 yrs
Sex	F>M	F=M
Associated Symptoms	• Headache • Scalp tenderness • Jaw claudication • Transient visual loss	None
Visual Acuity	<20/200 in >75%	>20/200 in >60%
Visual Field	Diffuse > Altitudinal	Altitudinal most common
Fundus	• Pallid edema • No "disc at risk" • Choroidal ischemia	• Hyperemic or pallid edema • Bilateral "disc at risk" • No choroidal ischemia
Natural History	• Rarely improves • Fellow eye in 54-95%	• Up to 40% improve • Fellow eye in ~ 20%
Fluorescein angiography	Disc and choroidal filling defect	Disc filling delay

GCA Ophthalmic Presentations



Serologic Features

Lab testing—while the mainstay in diagnosis is identification of inflammatory markers with a SED rate and C-reactive protein, other tests may yield additional, useful information

- CBC is useful in identifying co-morbid anemia
- CMP--Up to 20% of GCA patients can have elevated liver enzymes (2-4X increase)

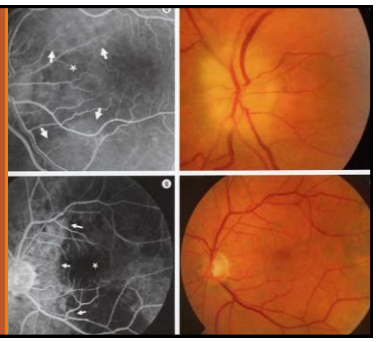
Vascular Features

IVFA

OCTA

Ultrasound

Flourescein and Photos



Non-arteritic anterior ischemic optic neuropathy versus cerebral ischemic stroke

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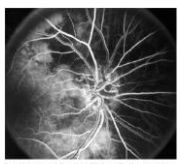
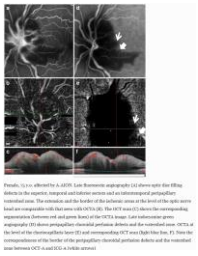
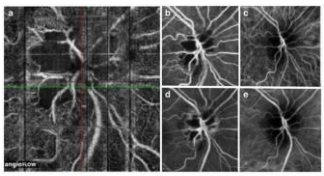


Delayed Choroidal Filling



Female, 74 y.o. affected by A-AION. Late fluorescein angiography (a) shows optic disc filling defects in the superior, temporal and inferior sectors and an intratemporal peripapillary watershed zone. The extension and the border of the ischemic areas at the level of the optic nerve head are comparable with that seen with OCTA (B). The OCT scan (C) shows the corresponding segmentation (between red and green lines) of the OCTA image. Late indocyanine green angiography (D) shows peripapillary choroidal perfusion defects and the watershed zone. OCTA at the level of the choriocapillaris layer (E) and corresponding OCT scan (light blue line, F). Note the correspondence of the border of the peripapillary choroidal perfusion defects and the watershed zone between OCT-A and ICGA-A (white arrows)

Using OCTA



Female, 73 y.o. affected by acute non-arteritic anterior ischemic optic neuropathy (NA-AION). OCT-A (A) shows ischemic defects in the superior and temporal optic nerve head sectors. The extension and the border of the non-perfusion areas on OCT-A are comparable with that seen in early and late fluorescein angiography images (B and D, respectively). Peripapillary choroidal delay is better visible with indocyanine green angiography images (C:early phase; E:late phase)

NAAION

Temporal Arterial Ultrasound

Cureus

Open Access Review Article

DOI: 10.7759/cureus.42350

Temporal Artery Ultrasound for the Diagnosis of Giant Cell Arteritis in the Emergency Department

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Abstract

Giant cell arteritis (GCA), known as temporal arteritis, is a serious condition requiring immediate treatment to prevent complications. GCA can be difficult to diagnose, especially in emergency department (ED) settings where ophthalmology and rheumatology services may be unavailable. Temporal artery ultrasound (TAUS) is a valuable tool for diagnosing GCA. In the ED, TAUS can be used to quickly rule out GCA and avoid unindicated steroid treatment, which can cause serious morbidity in elderly patients. This article discusses the use of TAUS for evaluating patients with suspected GCA in the ED and its potential to expedite treatment and ensure appropriate, timely follow-up for patients with this potential vision and life-threatening condition.

Normal Temporal Artery vs Halo Sign

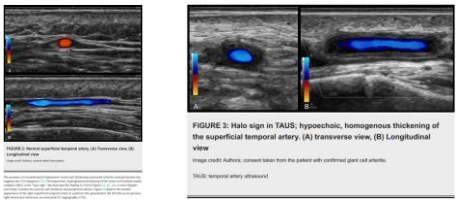


FIGURE 3: Halo sign in TAUS; hypoechoic, homogenous thickening of the superficial temporal artery. (A) transverse view, (B) Longitudinal view

Image credit: Authors; consent taken from the patient with confirmed giant cell arteritis.

TAUS: temporal artery ultrasound

TAUS vs CTA

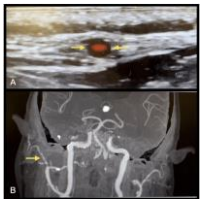
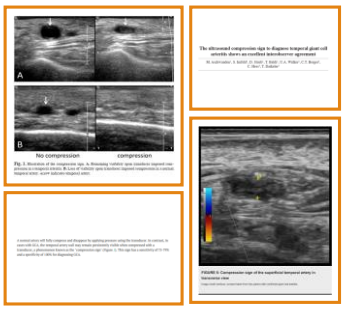


FIGURE 4: (A) Halo sign of the superficial temporal artery in an 89-year-old man with a history of polymyalgia rheumatica who presented to the ED with an acute painless right monocular vision loss and temporal tenderness. (B) Contrasted CTA revealed a beaded appearance of the right superficial temporal artery suggesting GCA.

Image credit: Authors; consent taken from the patient with confirmed GCA.

CTA: computed tomography angiography; GCA: giant cell arteritis

Compression Sign



Temporal Artery Biopsy

Temporal artery biopsy in the diagnosis of giant cell arteritis: Does the end justify the means?

Bowling K; Rait J; Atkinson J; Srinivas G.

Author information

Annals of Medicine & Surgery 20(p 1-5, August 2017) | DOI: 10.1016/j.amsu.2017.06.020

HIGHLIGHTS

- Of the 129 temporal artery biopsies performed 17 (13.2%) were positive for Giant Cell Arteritis.
- 83% of patients had an American College of Rheumatology score of 3 or more and would not be biopsied in America.
- Colour Duplex Ultrasound scan now offers a greater sensitivity and specificity for the diagnosis of GCA.

Results:

129 temporal arteries were biopsied with a total of 17 positive biopsy results. 10 biopsy samples were insufficient to confirm or refute GCA. 8 patients within the biopsies negative for GCA had their prednisolone therapy stopped. 5 patients had unknown follow up, with the remainder (89; 87.3%) of the patients continued prednisolone management for treatment of GCA for at least 6 weeks.

Conclusion:

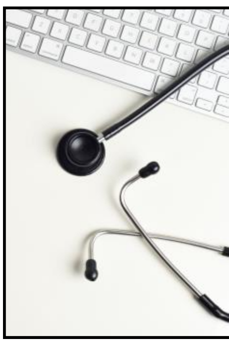
Overall 13.2% of our biopsies were positive for GCA and 87.3% of biopsy negative patients continued prednisolone therapy on clinical grounds. In the face of new diagnostic tests (high resolution MRI (Magnetic Resonance Imaging), colour duplex USS (Ultra Sound Scan) and PET (Positive Emission Topography) can we justify invasive surgery to all patients on histological grounds when the results may not alter management? Further investigation is needed directly comparing newer imaging modalities to histology.

Treatment: Giant Cell Arteritis

ACTEMRA tocilizumab for GCA

Arteritic patients need prompt, high-dose (preferably IV) corticosteroids to prevent involvement of fellow eye!!!

- Treatment can precede the TA biopsy by up to 2 weeks
- The FDA has also approved **ACTEMRA (tocilizumab)**, a monoclonal antibody that binds to interleukin-6 (pro-inflammatory cytokine) receptors. After starting patients on corticosteroids, this medication is administered in sub-cutaneous injections. The steroid dose is tapered at the same time. 56% had sustained remission at 52 weeks with weekly dosing; 53% with every other week dosing.
- GiACTA Trial--Compared to prednisone + placebo, patients taking tocilizumab had a significant improvement in sustaining remission and required lower doses of prednisone
- Treatment does not address the AION. Rather, it addresses the underlying etiology of the AION and is necessary to prevent other GCA complications, including involvement of the fellow eye.



Giant Cell Arteritis Fast Track Programs

Provide rapid multi-disciplinary evaluation, initiate appropriate therapy promptly, and facilitate innovative research in GCA.

Team of providers

- Rheumatologists
- Trained vascular technologists
- Cardiologists with a subspecialty in vascular medicine

Other specialists include neuro-ophthalmologists and vascular surgeons

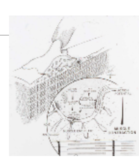
Goal is to rapidly and accurately diagnose GCA, leading to appropriate management and prevention of relapses

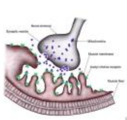
Myasthenia Gravis Update

Myasthenia Gravis

Autoimmune disorder

Antibodies attach near ACH receptors on muscles to block neuro-muscular transmission





Important Features

- Muscle weakness/fatigability
  - Variable
  - Worse later in the day
- Affects voluntary muscle
- Predilection for muscles innervated by cranial nerves

Presentation of Ocular Signs

10% present with ptosis only

90% present with ptosis and EOM weakness

25% have weak orbicularis muscles
- With or without the other signs

Ocular vs. Generalized MG

Ocular—eye muscles only

Generalized—occurs in muscle groups elsewhere in the body

Predilection for muscle groups innervated by cranial nerves, so assessing cranial nerves with motor functions is important

Proximal muscle groups are also vulnerable

Signs Suggestive of Generalization

Orofacial weakness (myasthenic snarl)

Swallowing, regurgitation of liquids, choking

Hoarseness

Slurred speech

Dyspnea

Neck/shoulder weakness

Tongue weaknesss

Proximal limb weakness; unstable gait

The neurologic exam in myasthenic patients should emphasize cranial nerves and motor testing. And don't forget about a good case history

Tensilon Test (Edrophonium)

Diagnostic

Edrophonium is administered intravenously and there is rapid improvement in skeletal muscle function in myasthenic patients due to interference with anticholinesterase

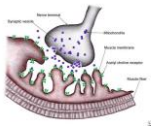
Ptosis tends to respond better; false positives common

Side effects rare but serious
- Tensilon is no longer available for diagnostic use
- Antibody testing has become the gold standard

Sleep test is in-office alternative

Serologic Testing

Acetylcholine Receptor Antibodies (AChR Ab)
- Blocking, Binding, Modulating subtypes
- Antibodies present in 90% with GMG but only 40-77% with OMG



Antibody testing can confirm the disease but cannot rule it out

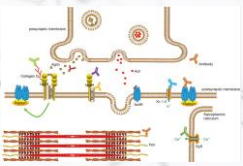
Other Antibodies

Anti-MuSK (muscle specific kinase) antibody
- Present in half of patients with negative AChR antibodies

Anti-Liproprotein receptor related protein (LRP4)
- Up too half of double seronegative (AChR/MuSK) MG patients are positive for this!!

Titin-Ab
- Indicates thymoma (95%)

RyR-Ab
- Indicates thymoma (70%)



Electrophysiologic Studies

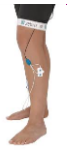
Recording the electrical activity of muscles can sometimes detect fatigability suggestive of GMG.

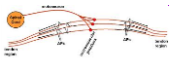
Repetitive stimulation (RNS)

- Normal in 50% OMG
- Reduced in most GMG

Single Fiber Stimulation

- More sensitive than RNS but may be less specific
- Can test orbicularis and levator for dx of OMG
- Helpful in seronegative MG and in predicting risk of generalization in OMG



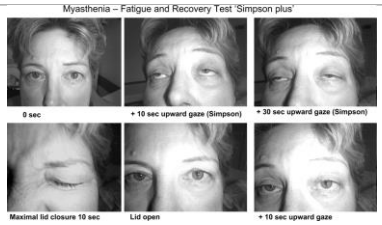


In-Office Diagnostic Tests

- Eyelid fatigue
- Pseudo-lid retraction
- Orbicularis weakness
- Sleep Test
- Ice-pack test

Eyelid Fatigue

Toyka KV: Neurology, 2006



Orbicularis Strength

The Sleep Test for Myasthenia Gravis

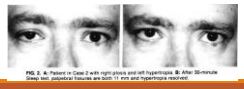
A Safe Alternative to Tensilon

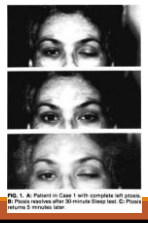
Jeffrey G. Odel, M.D., Jacqueline M. S. Winterkorn, Ph.D., M.D., and Myles M. Behrens, M.D.

Journal of Clinical Neuro-Ophthalmology; 1991

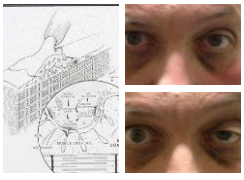
Improvement of signs after 30 minute nap

Return of presentation 30 seconds to five minutes after awakening





Ice-Pack Test
Sethi et al--1987

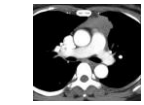


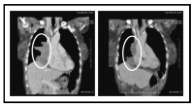
- Cooling reduces activity of AChE which increases available Ach
- Application for 2-5 minutes
- Positive when ptosis improves by at least 2mm

Once the Dx is Confirmed……..

Rule out autoimmune thyroid disease or other autoimmune disorders
- Dependent on additional presenting signs or symptoms
- Take a good history!

CT or MRI of Chest
- Rule out thymic hyperplasia or thymoma





Mediastinal Imaging

Two thirds of all general myasthenics have thymic hyperplasia

10-15% of all myasthenics have thymoma (Berrih-Aknin et al; 1987)

10% of patients have other autoimmune disease (more when thymic abnormality is present)

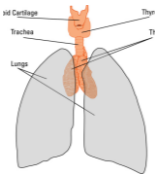
Prognosis is poorer with thymoma

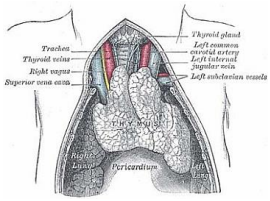
The Thymus Gland

Role in development of the immune system in early life

Large through puberty but then is replaced by fat in adulthood

May remain abnormal in myasthenics with clusters of immune cells





Myasthenia and the Thymus

Thymus gland may give incorrect instructions to developing immune cells
- Leads to autoimmunity and the production of the acetylcholine receptor antibodies
- Blockage of neuromuscular transmission.

Medical Management

Symptom Therapy
- AChE inhibitors (Mestinon)
- No long term effect on the immune activity of the disease
- Limited efficacy for diplopia

Immunomodulatory Therapy
- Induction and maintenance phases
- May have beneficial effect on rate of remission and severity
- May decrease incidence of generalization

Treatment Goal: Complete Remission

Symptomatic Therapy
- Acetylcholinesterase inhibitors (Mestinon)

Short term rescue immunotherapy
- Plasma Exchange
- IV immunoglobulin

Long term immunosupression

Immunomodulatory Agents

Corticosteroids
- Useful in OMG or mild GMG
- Can be used for up to two years
  - Gastric ulcer/osteoporosis
- Works well for ptosis or EOM limitations

Azathioprine
- Useful long-term option or when corticosteroids contraindicated

Cyclosporine
- Useful with incomeplete response or intolerance to corticosteroids
- Nephrotoxic; rheumatology must be involved

Mycophenolate
- Post organ transplant drug used off label for gMG

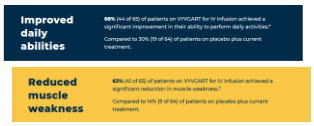
Tacrolimus
- used for prophylaxis of organ rejection post-transplant; off label for gMG

Monoclonal Antibodies
Rituxin; Eculizimab

Newer Treatment Option

VYVGART (efgartigimod alfa) intravenous infusion is an FDA-approved treatment for adults with anti-AChR antibody positive generalized myasthenia gravis (gMG).

The drug binds to and inhibits the neonatal Fc receptor, thereby reducing the levels of circulating IgG and pathogenic IgG autoantibodies, without altering other immunoglobulins (IgA, IgD, IgE or IgM) and without reducing albumin levels or increasing cholesterol levels



Another New Option

Rystiggo (rozanolixizumab)

Subcutaneous infusion

Monoclonal antibody approved for gMG

Anti-AChR and Anti-MuSK antibody positive adults

6-week treatment cycle

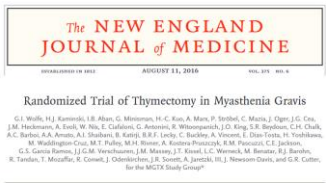
Thymectomy

Beneficial effect, even without thymoma

Response takes up to a year
- Full effect may not occur for 5 years

Improvement in up to 85%; remission in 35%

May be ok for OMG if resistant to other therapies



Conclusions

126 patients

Thymectomy improved clinical outcomes over a 3-year period in patients with nonthymomatous myasthenia gravis. (Funded by the National Institute of Neurological Disorders and Stroke and others

Thymectomy For MG

OMG

Thymectomy may improve symptoms AND prevent progression to GMG
- Kodama H, et al 1993

Thymectomy is not recommended as first line treatment
- Consider if patient is unresponsive to medical treatment or when tests indicate high risk of progression to GMG
- Kerty E, et al 2014

GMG

Thymectomy results in clinical improvement in AChR antibody-positive Mg patients
- Reduces the severity of the disease and in the required dosage of immunosuppressants

Further study is needed to establish efficacy and long-term outcome in juvenile and geriatric paitents and anti-MuSK antibody positive patients

Additional Treatments

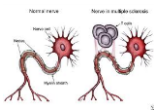
Plasmapheresis
- Removes abnormal antibodies from the blood
- Short term effects

Intravenous Immunoglobulin (IVIg)
- Provides normal antibodies to limit damage to the neuromuscular junction

Both are used for severe disease that is unresponsive to other therapies

Demyelinating Optic Neuritis

Typical Optic Neuritis



Caused by inflammatory demyelination of the optic nerve

Strong association with multiple sclerosis

Myelin sheath is the focus of the attack; but axons are also involved

Clinical Profile

Acute/subacute, unilateral vision loss of any magnitude is accompanied by pain and may be associated with a swollen or normal appearing optic nerve

Progression of symptoms for a week or less with visual improvement beginning within one month. Recovery is nearly complete with persistent residual deficits in function.

Visual field changes emphasize the central 30 degrees
- May be diffuse, altitudinal, arcuate or central loss within the central 30 degrees

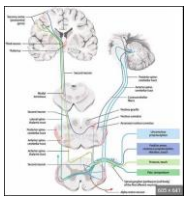
No evidence of any other associated systemic disorder or additional involvement

Inflammatory lesions in the brain seen in 59% (35% when the patient has no other clinical signs of MS)

MS and Optic Neuritis

Typical optic neuritis is strongly associated with MS
- Often, patients will report past symptomology that is consistent with MS, such as episodes of paresthesia, vertigo, balance problems, bladder control problems…

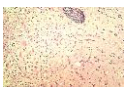
When it occurs in isolation and as a first clinical presentation (Clinically Isolated Syndrome, or CIS), the likelihood of definite MS increases with time and presence of MRI changes

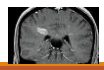


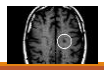
Two Characteristic Lesions

Inflammation
- Due to activated T-cells, B-cells and monocytes

Demyelination and axonal damage
- While demyelination is the main lesion, there is also some degree of axonal damage that leads to progression of disability
- Axonal damage is more problematic in more aggressive forms of the disease



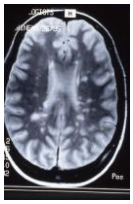




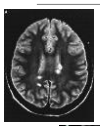
MRI and Optic Neuritis

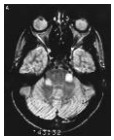
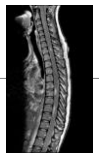
MRI is done for two reasons:
- To look for signs of CNS dissemination of the inflammatory process characterized by signal abnormalities in the white matter
- To rule out other causes of the optic neuritis

Signal abnormalities in 59% of the patients with acute optic neuritis
- Only 35% had abnormalities if no other clinical signs or sx of MS
- Lesions can also be seen in the spinal cord



Dissemination in Space



periventricular

infratentorial

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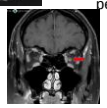
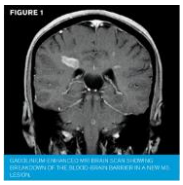
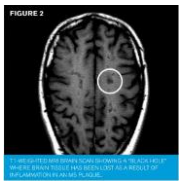

optic nerve

juxtacortical





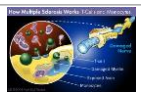
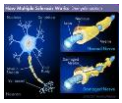
Dissemination in Time

Etiology

Auto-immune-mediated inflammatory demyelination is the primary problem with secondary axonal injury

Genetic influences are also present
- Susceptibility genes have been identified

Proposed theory is that patients have the genetic predisposition but a trigger is required to manifest the disease

Potential Triggers and MS

Viral infection may be the trigger that activates the T cells.
- Epstein Barr Virus found in higher association
- High expression of EBV antigens within MS plaques
- Causative role has been difficult to prove and it may be possible that EBV is an effect rather than a cause due to dysregulation of the immune system

Other potential triggers have been proposed
- Vitamin D deficiencies
- Smoking

Why Vitamin D?

Role in regulating immune response by decreasing production of pro-inflammatory cytokines and increasing production of anti-inflammatory cytokines

High vitamin D levels appear to be associated with reduced risk of MS
- This may be the reason why certain temperate populations have low prevalence

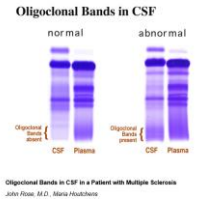
Lumbar Puncture in Dx of MS

Indicates chronic inflammation in CNS and rules out infection
- Only direct test to indicate chronic CNS inflammation

Useful when clinical findings and MRI are not conclusive
- double risk of MS when MRI is normal

"Oligoclonal Bands"
- Bands of immunoglobulin
- Present in 90-95% of MS patients

IgG
- B cells result in production of IgG
- 70-90% of MS patients



Oligoclonal Bands in CSF in a Patient with Multiple Sclerosis
John Rose, M.D., Maria Houtchens

Summary of Typical Optic Neuritis

Young, healthy adult; usually female

Sudden, unilateral visual loss with progression of symptoms for a week or less with visual improvement beginning within one month.

Vision loss is accompanied by pain and may be associated with a swollen or normal appearing optic nerve

No evidence of any other associated systemic disorder or additional involvement

Associated with multiple sclerosis

Other Demyelinating Optic Neuropathies

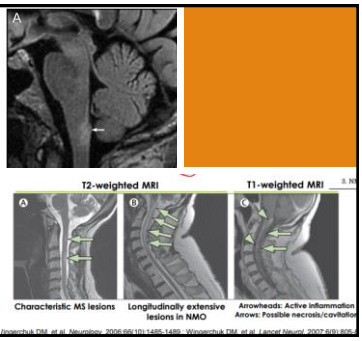
Two additional demyelinating disorders with identifiable immunoglobulin seromarkers should be considered in certain cases of optic neuritis

They also cause painful, demyelinating optic neuritis but they are caused by different disorders
- Neuromyelitis optica spectrum disorder
- Myelin oligodendrocyte

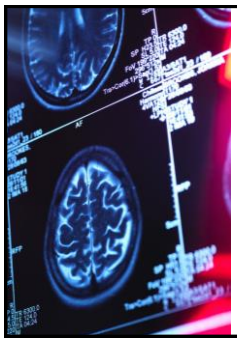
Neuro Myelitis Optica Spectrum Disorder (NMOSD)

Targets the optic nerves, spinal cord, and brain, but different areas of the brain than MS
- Diencephalon/medulla
- Chiasmal involvement

More severe presentation with poor visual prognosis (unlike MS), and poor disability prognosis
- Within 5 years, > 50% of NMO pts are blind in 1 or both eyes or require ambulatory help.
- Disability is influenced by number of relapses



Wingerchuk DM, et al. Neurology. 2006;66(10):1485-1489. Wingerchuk DM, et al. Lancet Neurol. 2007;6(9):805-



Distinguishable from MS By the Following

Clinical presentation
- More severe vision loss
- Can be bilateral
- Poorer recovery

MRI Findings
- Targets different parts of the CNS
- Longer spinal cord and optic nerve lesions

CSF Findings
- Pleocytosis
- No oligoclonal bands

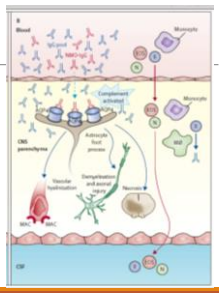
Comorbid Autoimmunity
- Up to 30%
- Myasthenia, Sjogrens, Lupus

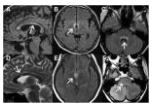
Pathophysiology

NMO IG attacks proteins of the AQP4 channels on astrocytes

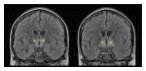
Immune reaction leads to demyelination

Diagnosis is confirmed serologically
- NMO-AQP4 antibodies

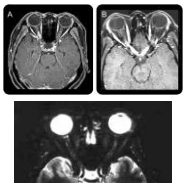




Comparison between the cranial magnetic resonance imaging features of neuromyelitis optica spectrum disorder versus multiple sclerosis in Taiwanese patients.



Magnetic resonance imaging in neuromyelitis optica

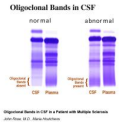


More MRI Findings

CSF Findings

MS

Oligoclonal bands



Oligoclonal Bands in CSF in a Patient with Multiple Sclerosis
John Rose, M.D., Reha Healthcare

NMOSD

No oligoclonal bands
- They may occur transiently at onset

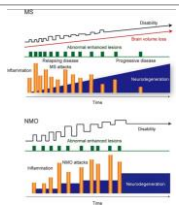
Pleocytosis
- Granulocytes
- Eosinophils

MS vs NMOSD Progression

Disability in MS can progress independently from relapse activity

Disability in NMO is dependent of relapse activity

Journal of Neurology, Neurosurgery, and Psychiatry. Kawachi I, Lassmann H, 88:137-145

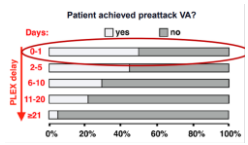


Treatment Delay In NMOSD Optic Neuritis Leads to Poorer Visual Prognosis

Plasma exchange early in the course of the disease leads to better visual outcomes

Treatment referrals must be immediate!!

Bonnan M, Valentino R, Debeugny S et al, ournа of neurology, Neurosurgery and Psychiatry



NMOSD Treatment is Different than MS Treatment

NMOSD has traditionally been treated with immunosuppressants. However, controlled studies have been lacking, and up to half of patients continue to experience attacks while receiving these therapies. The newly approved treatments are three monoclonal antibodies:

Eculizumab, a complement inhibitor

Inebilizumab, an anti-CD19 agent

Satralizumab, an anti-interleukin-6 receptor

Plasma exchange is used for acute attacks

When Serologic Testing is Negative...

Disease may be monophasic

Consider an alternate demyelinating optic neuropathy
- MOG

Myelin Oligodendrocyte Glycoprotein-Associated Disease (MOGAD)

Very aggressive and often bilateral (40%) optic neuritis with severe disc edema and hemorrhage

Patients are younger and less frequently female

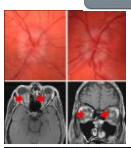
Involvement of optic nerves, brainstem and/or spinal cord

In children, encephalomyelitis is common

Very steroid responsive so much better visual prognosis than NMO

Monophasic in most cases

Diagnosed with MOG antibody testing



Reprinted from American Journal of Ophthalmology, 195, Chen JJ, Flanagan EP, Jitprapaikulsan J, et al.,

Certain MS Therapies can Aggravate NMOSD and MOGAD

Interferons

Fingolimod (Gilenya)

Natalizumab (Tysabri)

MS Treatment Update

Important Dates in MS Treatment

1993
Betaseron
First treatment for MS

2004
Tysabri
First monoclonal antibody infusion

2010
Gilenya
First Oral Medication

Traditional MS Therapy

First available in 1993

Reduced number of relapses

Reduced severity of relapses

Reduced development of new areas of inflammation seen on MRI

Evidence of delaying short-term disease progression

The Drugs:

Interferons—Immune modulators that have antiviral properties

Betaseron (Interferon beta-1b)

Extavia (interferon beta-1b)

Avonex (interferon beta-1a)

Rebif (Interferon beta-1a)

Copaxone (glatiramer acetate)

Immune modulator; blocks attacks on myelin

Side Effects

Outstanding and well established safety record

Most are well-tolerated

Flu-like symptoms	Worsening spasticity or depression

What's New with Traditional Therapies

Plegridy (peginterferon beta-1a)
- Available in 2014
- Pegylated molecular structure has longer half-life allowing for less frequent injections
- Administered every 2 weeks

Monoclonal Antibodies/Infusions

More aggressive immune suppression

Greater risks of complications

Increasingly **utilized as first line therapy when there appears to be more aggressive disease**

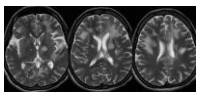
2004: First Monoclonal Antibody Infusion

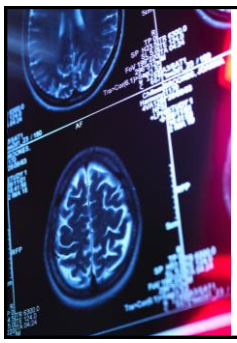
Tysabri (natalizumab)

Shortly after its use began, 4 MS patients developed progressive multifocal leukoencephalopathy (PML) and died
- Progressive inflammation of white matter
- Fatal in 30-50%

It was determined to be caused by comorbid dormant JC virus that was activated with immunosuppression

Careful monitoring of immune status has since been developed to ensure safety





Tysabri

- IV infusion Q 28 days
- Blocks migration of leukocytes into the CNS
- Robust benefits on relapse rate, disability and MRI progression
  - 70% reduction in relapse rate; 90% reduction in new disease activity on MRI
  - Significant decline in preventing worsening of disability
- High PML risk!
  - Must pretest for JCV
  - Strict prescribing guidelines (TOUCH program) that requires submission of immune status and JC status prior to drug renewals

Monoclonal Timeline

2004 Tysabri → 2014 Lemtrada → 2016 Zinbryta → 2017 Ocrevus → 2020 Kesimpta

Lemtrada (alemtuzumab)

- Two infusion courses one year apart
- Broad immunosuppressant
  - Uses an antibody that targets CD52
- Very Effective
  - 5 year data (CARE-MS I) shows 40% of patients had no evidence of disease activity from years 3-5
  - Response to the drug is maintained; most patients who are well at two years remain well at 5 years
- Careful monitoring necessary due to infection risk
- High rate of secondary autoimmunity
  - Thrombocytopenic purpora

Ocrelizumab (Ocrevus)

Humanized monoclonal antibody; similar to rituximab

Two IV treatments every 6 months

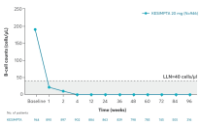
Rapid and pronounced effect on MS but higher risk of opportunistic infections

Positive results in both relapsing and primary progressive forms of MS

Daclizumab (Zinbryta)

Subcutaneous auto-injection; q4 weeks

Prevents activation of T-cells by disrupting interleukin-2 signaling



Ofatumubab (Kesimpta)

Used for relapsing and secondary progressive forms of MS

Monoclonal antibody to CD20 that appears to provide rapid B-cell depletion

Administered subcutaneously

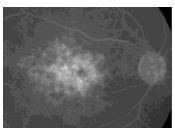
Oral Medications

Revolutionized treatment of MS due to their convenience

Similar efficacy or better compared with traditional therapies

Used when response to traditional meds is suboptimal, or when there are needle phobias

GILENYA™ (fingolimod) capsules 0.5mg



Gilenya (Fingolimod)

First oral medication

Sequesters lymphocytes in lymph nodes leading to 80% reduction of migration into CNS

Risk of PML is low, but evident
- Immune status must be monitored

Risk of zoster reactivation
- No live shingles vaccines

Higher dosages associated with macular edema

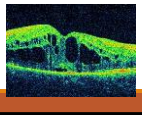
Gilenya and Macular Edema

- All patients have an increase in macular volume; small subset develop CME
  - Unclear whether it induces CME or unmasks pre-existing subclinical edema
  - Discontinuation of drug reverses the edema
- Highest risk in first year of treatment
- Macular OCT done prior to instituting therapy
  - OCT repeated at 3 months, followed by 6 months and then yearly

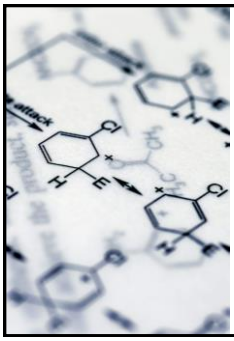
In the MS cohort it appears as though
- diabetes
- prior uveitis
- presence of a pre-existing epiretinal membrane
- other evidence of vitreoretinal traction

constitute the greatest risk for the development of macular edema, although diabetes was explicitly an exclusion criterion in the original MS clinical trials.

The rate of macular edema was officially reported at 0.2% at the approved dose of 0.5 mg/ day.



Newer Drugs in this Class



Tecfidera (dimethyl fumarate): 2013

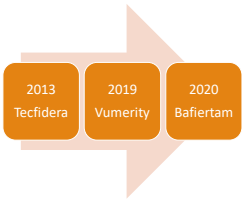
Reduces relapse rate by 50%

BID administration

Two Mechanisms:
- Depletes glutathione which leads to production of the anti-inflammatory stress protein heme oxygenase.
- Generates an antioxidant response via upregulation of the NRF2 pathway.

Greater risk of PML so more careful monitoring for lymphopenia

Newer Drugs in this Class



Vumerity (diroximel fumarate)
- Same active metabolite but different structure
- Fewer GI side effects

Bafiertam (monomethylfumarate)
- No prodrug is involved
- Just like Vumerity, there are fewer GI side effects

Aubagio (teriflunamide): 2012

Inhibits synthesis of pyramidines to block development of rapidly dividing lymphocytes

Once daily dosing

Modest efficacy; similar to interferons

No PML risk

Risk to offspring in both males and females of reproductive age

Mavenclad® (cladribine) is a newer purine antimetabolite for relapsing and secondary progressive disease. It targets B and T lymphocytes

Cyclophosphamide + Stem Cell Transplantation


Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis
A Randomized Clinical Trial