QUESTION 59

Therapeutic blockade of alpha 4 integrins is currently under clinical trial for several diseases. On the basis of known pathogenesis, patients with which one of the following conditions are most likely to receive benefit from this treatment?

A. Migraine  
B. Stroke  
C. Multiple sclerosis  
D. Alzheimer’s disease  
E. Epilepsy

Answer is C – note this is the only condition that has an immunological basis. Alpha 4 integrins are adhesion molecules which help T cells pass through capillary walls.

DEMYELINATING DISORDERS

- Characterised by inflammation and selective destruction of CNS myelin  
- Peripheral NS is spared

MULTIPLE SCLEROSIS

- Characterised by a triad of:  
  o Inflammation  
  o Demyelination  
  o Gliosis (scarring)  
- Can be relapsing-remitting or progressive  
- Manifestations can vary greatly from mild to rapidly evolving and incapacitating

PATHOGENESIS

- Acute lesions are characterised by perivenular cuffing with inflammatory cells (mainly T cells and macrophages) which also infiltrate the surrounding white matter  
- BBB is disrupted but vessel wall is preserved  
- In >50% of cases, myelin-specific autoantibodies promote demyelination and stimulate macrophages and microglial cells  
- As lesions evolve, astrocytes proliferate (gliosis)  
- Surviving oligodendrocytes may partially remyelinate the surviving naked axons – shadow plaques

PHYSIOLOGY

- Normal nerve conduction in myelinated axons occurs in saltatory manner – action potential jumps from one node of Ranvier to the next  
- This allows much faster conduction  
- Following demyelination, conduction block can occur due to hyperpolarisation of the exposed segment (due to exposure of voltage-dependent K channels)  
- This block is temporary – sodium channels which are normally localised at the nodes redistribute along the demyelinated segment and allow conduction

EPIDEMIOLOGY

- Female > Male (approximately 2:1)
- Age of onset typically 20-40yrs
- Rarely can begin as early as 2yrs or as late as 70s
- There is a genetic susceptibility to MS
  - Increased risk if relative has MS
- MHC class II is one area associated with MS susceptibility

IMMUNOLOGY

- Autoimmune cause for MS has support but not proven
- Autoreactive T cells directed against components of myelin
- Evidence to support this theory includes:
  - Inflammation with disruption of BBB seen in early stages of demyelinating lesions
  - T cells, B cells and macrophages seen on histology
  - Increased oligoclonal IgM and IgG in CSF
  - Myelin reactive T cells found in MS plaques, in CSF and in peripheral circulation
  - Th 1-type immune activation is a feature (as marked by IL12, IL18)
  - Risk of developing MS linked with class II MHC
  - Immunomodulatory drugs that reduce Th1 response can reduce disease activity
  - Myelin basic protein (MBP) is an important T cell antigen in experimental allergic encephalomyelitis and probably also in humans
  - Activated MBP-reactive T cells are often found in CSF of MS patients
  - Autoantibodies directed against myelin (such as myelin oligodendrocyte glycoprotein) probably act with T cells to cause demyelination
- Viral infections could possibly stimulate the immune system to cause MS (EBV has been considered)
- Also genetic and environmental factors

CLINICAL MANIFESTATIONS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percent of Cases</th>
<th>Symptom</th>
<th>Percent of Cases</th>
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</thead>
<tbody>
<tr>
<td>Sensory loss</td>
<td>37</td>
<td>Lhermitte</td>
<td>3</td>
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<tr>
<td>Optic neuritis</td>
<td>36</td>
<td>Pain</td>
<td>3</td>
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<tr>
<td>Weakness</td>
<td>35</td>
<td>Dementia</td>
<td>2</td>
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<td>Paresthesias</td>
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<td>Visual loss</td>
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<td>15</td>
<td>Facial palsy</td>
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<td>Ataxia</td>
<td>11</td>
<td>Impotence</td>
<td>1</td>
</tr>
<tr>
<td>Vertigo</td>
<td>6</td>
<td>Myokymia</td>
<td>1</td>
</tr>
</tbody>
</table>
Paroxysmal attacks | 4 | Epilepsy | 1
| Bladder | 4 | Falling | 1

Harrison’s (http://www.accessmedicine.com/content.aspx?aID=106923)

Features Suggestive of MS
- Relapses and Remissions
- Onset between 15 and 50 years
- Optic neuritis
- Lhermitte’s sign
- Internuclear ophthalmoplegia
- Fatigue
- Uhthoff’s phenomenon

Features not Suggestive of MS
- Steady progression
- Onset before age 10 or after age 50
- Cortical deficits such as aphasia, apraxia, alexia, neglect
- Rigidity, sustained dystonia
- Convulsions
- Early dementia
- Deficit developing within minutes

Optic Neuritis
- Most common type of involvement of visual pathways
- Usually presents with acute or subacute unilateral eye pain that is accentuated by ocular movements
- Followed by variable degree of visual loss affecting mainly central vision
- Bilateral simultaneous ON rare in MS, suggests alternative diagnosis
- Afferent pupillary defect may be found
- May see disc oedema if head of optic nerve involved, or can be normal fundus examination in acute setting
- Later optic disc becomes pale due to axonal loss and gliosis
- 90% of patient regain normal vision over 2-6 months
- Progression to MS ranges from 15 to 75%

Internuclear Ophthalmoplegia
- This refers to abnormal horizontal ocular movements with lost or delayed adduction and horizontal nystagmus of the abducting eye
- Caused by a lesion of the medial longitudinal fasciculus on the side of diminished adduction
- If bilateral, usually get vertical nystagmus on upward gaze
- Bilateral INO is most suggestive of MS but can also be seen with intra-axial brain stem lesions (including Wernicke’s encephalopathy)
- Other common gaze disturbances in MS include
  - Horizontal gaze palsy
  - “One and a half” syndrome – horizontal gaze palsy plus INO
Motor Symptoms
- Paraparesis or paraplegia due to lesions in descending motor tracts
- Usually have UMN signs
- Asymmetrical
- Occasionally reflexes are reduced due to lesions of the reflex arc at a segmental level

Sensory Symptoms
- Paraesthesias (pins and needles, burning, pricking etc) and hypesthesias (reduced sensation)
- Pain is a common symptom
- Reflect spinothalamic, posterior column or dorsal root lesions
- Lhermitte’s symptom is the electric shock-like sensation that radiates down the back into the legs; evoked by neck flexion (can also occur with disorders of C spine)

Heat Sensitivity
- Neurological symptoms produced by an elevation of the body’s core temperature
- Eg: transient blurred/loss of vision which occurs during a hot shower or with physical exercise (Uhthoff’s symptom)
- Also fever can cause similar effects (pseudo-relapse)

Coordination
- Ataxia usually manifests as cerebellar tremors
- Slurred speech
- Failure of fixation suppression suggest cerebellar or cerebello-vestibular connection dysfunction

Bladder/Bowel Dysfunction
- Urgency is most common
- Urinary incontinence becomes more common as disease progresses
- Constipation more common that faecal incontinence
- Sexual dysfunction also common

Cognitive Dysfunction
- Memory loss, impaired attention, difficulties with problem solving, slower information processing, problems shifting between tasks
- Impairment sufficient to impede daily activities is rare

Vertigo
- Can appear suddenly
- Commonly associated with cranial nerve abnormalities such as facial numbness, diplopia, hypoacusis

Nystagmus
- Pendular nystagmus can occur
Year 2004 Paper two: Questions supplied by Megan

- Usually develops later in course

Epilepsy

- More common in patients with MS than in the general population
- Can be tonic-clonic or partial

Paroxysmal Symptoms

- Brief duration (30 sec to 2 min) and high frequency (5 to 40/day)
- No change in consciousness
- Self limiting course (weeks to months)
- Include Lhermitte’s symptom, tonic contraction of a limb, face or trunk, paroxysmal dysarthria/ataxia, paroxysmal sensory disturbances

DISEASE COURSE

Relapsing/Remitting MS

- 85% of cases
- Discrete attacks generally evolve over days to weeks
- Often there is complete recovery over ensuing weeks to months

Secondary Progressive MS
- Always begins as RRMS
- At some point, clinical course changes so that there is steady deterioration unassociated with acute attacks (which may continue or cease during this phase)
- 50% of pts with RRMS will develop SPMS after 15 years

**Primary Progressive MS**

- 15% of cases
- No attacks but steady decline
- Onset usually later in life
- Disability develops faster

**Progressive/Relapsing MS**

- 5% of cases
- Steady deterioration from disease onset
- Occasional superimposed attacks

**DIAGNOSIS**

Basically you need evidence of involvement of 2 or more areas of CNS (either acute attacks or progressive), mainly involving the white matter and not attributable to another disease. “Multiple in time and multiple in space”.

Definite MS if all 5 criteria fulfilled
Probable MS if all 5 criteria fulfilled except a) only one objective abnormality despite two symptomatic episodes or b) only one symptomatic episode despite two or more objective abnormalities
At risk for MS if criteria 1,2,3 and 5 fulfilled; patient has only one symptomatic episode and one objective abnormality

**MRI**

- Characteristic abnormalities found in >95% of patients with MS
- Multifocal hyperintense lesions on T2 weighted images involving brain, brain stem and spinal cord
- Burden of disease has weak correlation with clinical disability
- May see dark holes on T1 images corresponding to some of the hyperintense lesions on T2
Evoked Potentials

- Measure CNS electric potentials evoked by repetitive stimulation of selected peripheral nerves or of the brain
- Best to test a pathway that is not clinically involved
- Abnormalities of one or more EP modalities occur in 80 to 90% of patients with MS
- Seem to test visual EPs most often at Austin but can also do auditory, somatosensory and motor

CSF
- Protein usually slightly elevated
- Oligoclonal bands (2 or more found in 75 to 90% of patients with MS)
- Mild mononuclear pleocytosis common

PROGNOSIS
- Most patients have progressive neurological disability
- At 15 years from diagnosis only 20% have no functional limitation
- After 25 years 80% will require assistance to ambulate
- Difficult to determine prognosis for an individual
- Good prognostic factors include
  - ON or sensory symptoms at onset
  - Those who recover completely from an acute attack
  - <40yrs at onset (but not childhood)
  - Women
  - RRMS
  - <2 relapses in first year
  - Minimal impairment at 5 years
- Poor prognostic features include
  - Truncal ataxia
  - Action tremor
  - Pyramidal symptoms
  - Progressive course without relapses
- <20% of patient have a benign course and never develop neurological disability
- Pregnancy seems to lessen attacks, but more frequent attacks in post-partum period

TREATMENT

Acute Relapses
- Establish whether really an acute relapse or due to infection/fever or depression (pseudo relapse)
- Mild relapses do not require treatment (other than symptomatic treatment)
- Moderate relapses (some disability and symptoms have become unpleasant or are worsening) – prednisolone 75mg daily for 4 days then 25mg daily for 4 days
- Severe relapses (including ON with severe visual loss, paraplegia or brainstem symptoms) – admit and give methylprednisolone 1g IV daily for 3 days (or 0.5g daily for 5 days)
- In patients who continue to deteriorate despite treatment, plasmapheresis should be considered
- May reduce severity and duration of acute attacks but not effect on long-term disability

Treatment of Underlying Disease
- Immunomodulators generally first line and immunosuppressants second line
- May reduce attack frequency and slow progression but do not reverse symptoms or arrest disease
Immunomodulators

- Requirements for PBS subscription are
  - Relapsing-remitting MS
  - Ambulatory patient
  - 2 or more attacks in 2 years
  - Confirmation of the diagnosis by MRI
- Currently available immunomodulators
  - Interferon beta-1b (s/c 2nd daily)
  - Interferon beta-1a (IM weekly)
  - Glatiramer acetate (s/c daily)
  - Natalizumab (IV monthly)
- Interferon beta reduces the frequency and severity of attacks and the number and size of lesions on MRI
- Unknown if there is any effect on long term disability
- Minority of patients develop neutralising antibodies – if persistent may need to change drug or add immunosuppressant
- Glatiramer acetate has similar effects to interferon beta
- Natalizumab (monoclonal antibodies against alpha4-integrins) selectively inhibits adhesion molecules (alpha4-integrins), slowing the entry of T cells through cerebral capillaries
- Reduces relapses, new lesions and disability
- Used in patients intolerant or not responding to other immunomodulators
- Risk of PML (quoted as 1 in 1000 but not convincing evidence of a link)

Immunosuppressants

- Used for some pts with primary progressive or secondary progressive MS or those who have not responded to immunomodulators
- Dangerous if pt has recurrent UTIs, need to weigh up risks and benefits
- Methotrexate may reduce progression (limited trials); monitor FBE, LFTs
- Azathioprine seems to have similar benefits to immunomodulators; monitor FBE, LFTs
- Mitozantrone is a chemotherapy agent which helps stabilise the disease in severe and progressive cases
- More likely to help in pts still having some relapses or who have inflammation on MRI
- Risk of cardiotoxicity as well as all the usual chemotherapy risks
ADEM

- Acute demyelinating encephalomyelitis
- Monophasic course
- Frequently associated with antecedent viral infection (especially measles) or vaccination (especially smallpox or rabies)
- Hallmark is widely scattered small foci of perivenular inflammation and demyelination
- Immune response to MBP can be detected in most patients
- If severe, onset is abrupt and progression is rapid (hours to days)
- Fever, headache, meningism, lethargy, coma, seizures, may be signs of disseminated neurological disease
- Elevated CSF protein and lymphocytes generally ~200 cells occurs in 80%
- Initial treatment = high dose steroids
- Consider plasma exchange or IV Ig if refractory
- Prognosis variable, 5 to 20% mortality with measles encephalomyelitis
### Category A

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

### Category B1

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. (Animal studies submitted in support of new drug applications must conform to the Australian Guidelines on the Registration of Drugs - Volume 1, Prescription and Other Specified Drug Products, 2nd edition.)

### Category B2

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. (Animal studies submitted in support of new drug applications must conform to the Australian Guidelines on the Registration of Drugs - Volume 1, Prescription and Other Specified Drug Products, 2nd edition.)

### Category B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. (Animal studies submitted in support of new drug applications must conform to the Australian Guidelines on the Registration of Drugs - Volume 1, Prescription and Other Specified Drug Products, 2nd edition.)

### Category C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

*Note that Category C in the Australian and Swedish Categorisations of Risk is a pharmacological effect category and differs from that in the FDA Categorization (where Category C indicates greater likelihood of risk than in B on the basis of adverse effects of any type in animal studies).*

### Category D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

### Category X

Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.