

Homework 5: Differential Diagnosis of Multiple Sclerosis

Due Wednesday, 3/3/99

1.0 Background

Multiple Sclerosis affects approximately 350 K Americans and is the leading nontraumatic source of neurologic disability in young and middle-aged adults. MS causes *demyelination*: degeneration of the myelin sheath that insulates long tracts in the central nervous system (CNS) and the white matter of the brain.¹ Demyelination affects the tracts ability to transmit nervous impulses. Loss of the myelin sheath can have a positive or negative effect on conduction. Conduction can be slowed or completely blocked due to the loss of the myelin sheath. The loss of the sheath also creates the opportunity for spontaneous generation of nervous impulses or crosstalk between adjacent tracts.

The effect of MS is a constellation of CNS abnormalities including: fatigue, focal weakness, incoordination, loss of vision, vertigo, sensory loss, hearing loss, impotence, incontinence, and/or facial palsies.

The normal diagnostic criterion for MS is as follows:

1. Examination must reveal objective abnormalities of the CNS (not patient-reported).
2. The CNS abnormalities must be commensurate with lesions of the white matter tracts.
3. These abnormalities must implicate two or more areas of the CNS.
4. The pattern of manifestation must consists of either
 - a) two or more separate episodes of worsening involving different sites of the CNS, each lasting at least 24 hours and occurring at least 1 month apart
 - or
 - b) a gradual or stepwise progression of the disease over at least 6 months accompanied by increased CNS synthesis of IgG (immunoglobulin).
5. Age of onset is between 15 and 60 year of age.
6. The patient's neurologic symptoms cannot be attributed to other diseases.

In this problem set, we will assume that the patient exhibits neurologic symptoms that are commensurate with MS (criteria 1-5) and with the diseases named in the next section. We

1. The white matter is "white" due to the presence of myelin.

will assume that the “obvious symptoms” for competing disorders are We will focus our attention on criteria 6 and develop an expert system that uses laboratory and clinical tests to rule out competing disorders.

2.0 Diagnostic studies

1. MRI of the brain: gives us very nice pictures of the brain and provides objective evidence that something abnormal is going on. For the purposes of the exercise, there are only two portion of the brain that matter: grey matter (the actual cell bodies) and white matter (the cell tracts-the myelinated part).

2. Lumbar puncture (or the so-called spinal tap): Needle goes into back, pushes into the spinal canal and cerebrospinal fluid (CSF) comes out. CSF is a clear fluid that envelops the entire central nervous system, from brain to spinal cord. CSF can be sent for many, many different studies.

3. Blood tests: There are a lot of blood tests available.

4. Cerebral angiogram: contrast dye is squirted into a patient’s carotid arteries and all of their intracranial blood vessels light up. Used to be used a lot before the advent of the MRI, but now considered too risky except in some cases where it can provide supplemental info..

5. Chest Xray: enough said.

6. Arthritis: Several diseases are associated with joint pain. The normal frequency of some form of arthritis is approximately 2-3% for adults under 45, 30% from 45 to 65 and 70% over 65.

3.0 Competing Disorders

For this problem set, we will assume that the differential diagnosis of the patient includes just the following diseases:

- 1. Multiple Sclerosis** (incidence 150/100000)
- 2. Neurosyphilis** (incidence 100/100000): The late stages of syphilis cause neurologic deficits. Syphilis is usually sexually transmitted and is caused by *Treponema pallidum* subspecies *pallidum*.
- 3. CNS vasculitis** (incidence 10/100000 without autoimmune; 100/100000 with autoimmune): CNS vasculitis is inflammation of small and medium sized blood vessels in the brain. It may be a primary manifestation or secondary to autoimmune disorders such as **Sjogren’s disease** or **Systemic Lupus Erythematosis** (commonly called SLE or Lupus).
- 4. Neurosarcoidosis** (incidence 10/100000): Sarcoidosis is an autoimmune disease that causes granulomas (small balls of a special type of white blood cells usually formed

around a foreign body or infectious particle) to spontaneously form in the body. The usual sites of manifestation are the lungs, heart, and liver. Involvement of the brain is possible but rare.

5. **Progressive Multifocal Leukoencephalopathy (PML)** (5/100000): PML is a disease caused by the JC virus. PML is usually seen in patients that are immunocompromised such as AIDS patients or transplant patients (particularly patients with bone marrow transplants).
6. **Lyme disease** (50/100000): Lyme disease is a disease transmitted by ticks. Only around 50% of people actually remember a tick bite. Approximately, the same percentage remember the characteristic rash (bullseye). A fair number go on to experience flu-like symptoms in association with headache and stiff neck. About 15% of these develop neurologic symptoms like facial nerve palsies. If it remains untreated, some of these people go on to develop seizures, dementia, and/or a demyelinating syndrome resembling multiple sclerosis.

4.0 Diagnosis

4.1 Multiple Sclerosis

Epidemiology. MS is approximately twice as common in females than in males. The prevalence of MS is higher in caucasian populations. Although MS is extremely rare in Japan and is essentially unknown among black Africans, Japanese Americans and African Americans are at significant risk for developing the disease. The prevalence rates for African Americans and Japanese Americans are estimated at 1/4 to 1/3 that of Caucasian Americans. The disease incidence rate increases from adolescence through aged 35 and declines gradually thereafter. Incidence is approximately 250/100000.

Lumbar puncture.

1. Mononuclear pleocytosis (increase in white blood cells in the CSF): Mononuclear pleocytosis (> 5 cells/ μL) is present in 25% of MS patients (the normal number is ≤ 1 cell/ μL). Cell counts are generally less than 20/ μL for MS and counts above 50/ μL are unusual, but may occur at the onset of disease. Pleocytosis of > 75 cells/ μL or a finding of polymorphonuclear leukocytes in CSF is extremely unlikely (tends to rule out MS).
2. The fraction of *IgG* (immunoglobulin or antibodies) in the total amount of CSF protein is increased in 80% of patients.
3. Occasional MS patients exhibit mild increases in total CSF protein level.
4. *Oligoclonal banding* of CSF *IgG* may occur in MS patients. Two or more oligoclonal bands are found in 75 to 90 percent of MS patients.

MRI. An MRI image will show a number of small lesions in different areas of the white matter in the brain. MS is 10-12 times more likely in a patient with multiple white matter

lesions than in a patient with none. As MS is a disease of the nerve tracts, grey matter is not involved.

4.2 Neurosyphilis.

Epidemiology. Syphilis is caused by sexual contact with infectious lesions. Between 1977 and 1982, approximately half of all patients with syphilis were homosexual or bisexual men. With changing sexual practices due to HIV, this fraction has decreased. The most recent epidemic (1989 to 1993) predominately involved black heterosexual men and women and occurred mostly in urban areas (the disease seems to be highly correlated with the exchange of sex for crack cocaine). The incidence of syphilis is higher in black populations than in other ethnic groups. There is a striking increase in incidence rates in the southeastern United States.

Interestingly, half of the patients in mental institutions at the turn of the century (the *last* turn of the century, that is) were actually sufferers of late syphilis which can cause symptoms resembling schizophrenia.

Patient History: Neurosyphilis usually manifests a few months to up to 20 years after the initial infection. This is a late manifestation of syphilis implying that a diagnosis of primary (the genital lesion) or secondary syphilis (rash localized to the palms and the soles of the feet) was never made.

Blood tests:

1) Serologic test for syphilis (VDRL): The sensitivity of the VDRL test on serum (blood) is 71%. The specificity of the test (probability that the test is negative given that the disease is absent) is 97-99%. VDRL may be positive in cases of autoimmune disorders (1-20% of cases), SLE (11-20% of cases) or elderly patients (9-11%). In some cases the VDRL test is positive when Lyme disease is present (6%).

2) FTA-*Treponema*: FTA-ABS is a looks for antibodies specific to *T. pallidum*. In late neurosyphilis:

- a) FTA-ABS will be positive in 96% of cases.
- b) The false positive rate is approximately 1-3%.

Lumbar puncture. The CSF will almost always manifest increased protein levels (90%) or increased white blood cell activity (90%). VDRL in the CSF is positive 80% of the time and is highly specific.

MRI: Extensive white and grey matter changes can be seen in neurosyphilis. These changes are pretty non-specific

4.3 CNS Vasculitis

We are clustering together a number of diseases that cause CNS vasculitis: inflammation of blood vessels in the brain. These disease include primary CNS vasculitis (not accompa-

nied by any systemic manifestations) or CNS vasculitis seen in association with a systemic autoimmune disease such as lupus or Sjogren's disease.

CNS Vasculitic diseases

Lumbar puncture. Increased protein in 50% of cases and mononuclear pleocytosis (increased WBC) in 30% of patients. Oligoclonal bands in IgG may be found as well as an increased fraction of IgG in CSF protein.

Angiogram: The angiogram is a relatively risky procedure and is usually used when other tests do not reveal the cause of disease. Angiography is the most sensitive neurodiagnostic study for vasculitis. In 90% of cases of patients with vasculitis, the angiograph will show single or multiple areas of beading along the course of a vessel, abrupt vessel termination, hazy vessel margins and neovascularisation. (say "positive for vasculitis").

MRI. Many abnormalities are possible ranging from enhancing arteries through mass lesions, including lesions in white matter as well as the grey matter.

Blood tests: (Erythrocyte sedimentation rate) ESR is elevated for most autoimmune diseases (90% of time), but its selectivity is also high (70%).

Arthritis: Autoimmune diseases often cause arthritis (60% of time).

Chest Xray: abnormal in 20% of cases of CNS vasculitis seen with a systemic autoimmune disease

Blood tests. A high erythrocyte sedimentation rate (ESR) will be high in when CNS vasculitis is present. Specific antibody tests will be positive in 95% of patients with CNS vasculitis associated with specific autoimmune disorders. These tests are also highly selective with a selectivity of 98-100% depending on the disease.

4.4 Neurosarcoidosis

Epidemiology. The incidence rate for sarcoidosis is 10 to 15 times higher in blacks than whites in the United States. 75% of cases first occur in individuals less than 40 years of age.

MRI: In cases of neurosarcoidosis, there may be multiple lesions present in the brain mimicking MS.

Chest Xray: 90% abnormal.

Kveim-Stilzbach Skin Test: 75% sensitivity, 95% selectivity.

Blood tests: Elevated Angiotensin converting enzyme in 60% of patients with a 5% false positive rate.

Lumbar puncture: 80% of patients with CNS involvement will have elevated angiotensin converting enzyme levels in the CSF.

Arthritis: 25-50% of patients.

4.5 Progressive Multifocal Leukoencephalopathy (PML):

History: The patient will usually be immunocompromised. This includes transplant patients (particularly bone-marrow patients) and patients with HIV.

MRI: Lesions of the white matter usually symmetric in distribution. Grey matter is not involved.

Lumbar puncture: PCR Tests will reveal JC virus DNA 90% of the time (100% specificity).

4.6 Lyme disease

Arthritis. Lyme disease causes arthritis in 60% of cases.

Lumbar puncture. Increased protein in 50% of cases and very elevated WBC (100/ μ L) in 80% of patients. CSF antibodies to *B. Burgdorferi* are present in 45% of cases. Syphilis may also cause a false positive for this test (10% of the time).

Blood tests: Serum antibodies to *B. Burgdorferi* are present in 90% of cases, but are present in *severe cases* (such as the ones that cause neurologic disorders) a very high percentage of the time (say 98%). Syphilis may also cause a false positive for this test (20% of the time).

MRI: may show white matter changes in the area of the brain surrounding the ventricles.

5.0 Your assignment

1. (20) Describe your basic approach for constructing the model. Describe any assumptions that you plan (or need) to make.
2. (20) Draw the graphical model for this domain.
3. (60) Construct the graphical model using a probabilistic expert system tool.
4. (20) Develop a test case for each of the diseases and test your expert system on that test case. What is the differential diagnosis for each case?

Up to 20 points of extra credit will be granted to those students who increase the fidelity of the model using information drawn from experts or other sources.

You will deliver this expert system to your instructor so that he can examine and test it. We will critique all of the expert systems in class, so please turn in your assignment promptly.