

Re-Emerging Infectious of the CNS
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This symposium has several main objectives:

1. Demonstrate the global burden of disease and the disproportionate amount of infectious diseases that track with poverty, many of which, secondary to immigration and travel, must be diagnosed and treated in North America.
2. Highlight four infectious diseases affecting the CNS that are seeing global, local, or epidemic burdens increase in recent years.
3. Provide the working neuropathologist with a list of tools and resources to approach these and other difficult infectious diagnoses within the CNS.

Re-Emerging Infections
 of the Central Nervous System

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WorldMapper© view of dollars spent on public health...

World Mapper is a data viewer (www.worldmapper.org) that plots different statistics proportionately on a global map. There are many dozens of maps available which are related to healthcare. In this particular view, the dollars spent on public health by each country are shown. When the total dollars spent is largely disproportionate to the population size (e. g. Africa, India, and China), situations of massive healthcare disparity occur.

Several other World Mapper views are included at the end of this handout that show similar patterns for the burden of malaria, the number of doctors, etc. Within the context of central nervous system diseases, infections represent a small portion relative to the whole because the dollars spent on public health (which is an inverse metric for the burden of infectious diseases overall) reduce infections to rarities. In the modern world, a family from Africa who has lived in abject poverty can be in New York or Atlanta in less than 24 hours, bringing with them quiescent infections that may not present for weeks to years later. Rapidly expanding economies in India and China have newly wealthy business travelers and their families moving around the globe at rapid rates. Thus, as we consider the ever expanding human population, we must remember that when we view data presented above, that those dollars spent are only benefiting/injuring long term inhabitants of a country. © Copyright 2006 SASI Group (University of Sheffield) and Mark Newman (University of Michigan).

WHO (2002)	Americas	Europe	W Pacific	SE Asia	Middle East	Africa
Population (millions)	920	670	1110	2100	610	810
Cardiovascular	115	120	50	100	10	10
Cancer	115	120	50	100	10	10
Pulmonary	115	120	50	100	10	10
Musculoskeletal	115	120	50	100	10	10
Infectious	115	120	50	100	10	10
Diabetes/Metabolic	115	120	50	100	10	10
Digestive	115	120	50	100	10	10
Neurodegenerative	115	120	50	100	10	10
Conjunctive	115	120	50	100	10	10
Other	115	120	50	100	10	10
Total	115	120	50	100	10	10
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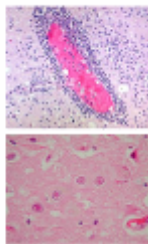
From the WHO's 2002 data on population and DALYs (Disability Adjusted Life Years), we see the effects of the public health spending (and other health metrics) reflected in the massive differences in types of disease burden in different continents and regions. DALYs are not only life years lost when a person dies but effective life years lost due to disability. North Americans are very familiar with the

leading healthcare issues in their own continent with DALYs lost attributed to neuropsychiatric, cardiovascular, cancer, pulmonary, and musculoskeletal diseases primarily (with accidents also contributing non-medical causes). The burden of infectious diseases in the Americas, Europe, and the Western Pacific is fourth or fifth

overall when considered as a group but individually never contribute more than 3%. In Southeast Asia, the Middle East, and Africa, we see the opposite with a third to 61% of all DALYs lost attributed to infectious diseases; moreover, as a category, infectious diseases dominate in these three regions. On an individual basis, malaria, HIV, and respiratory infections make up nearly 40% of the DALYs lost in Africa. These data are now 7 years old and there are many campaigns to reduce this deficit including ARV treatment for HIV, malaria control, vaccination, and elimination programs, and individual health treatment initiatives such as the Millennium Villages Project, Partners in Health, MSF, etc. However, economy is moving faster than these programs and the drive for peoples from these effected regions to move to other countries (especially North America) means that infectious diseases endemic in these countries are “emerging.”

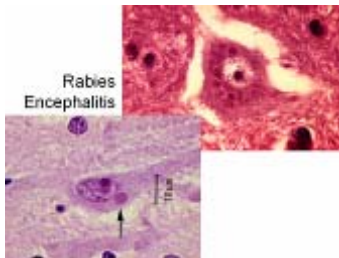
Viral CNS Infections

- Diagnosis is largely clinical with additional serological and/or CSF diagnostic tests including cytology
- Surgical biopsies are rarely required and should be avoided; however, autopsy confirmation of suspected clinical viral diagnoses is remains important for public health



Viral infectious of the CNS are by and large diagnosed on clinical grounds due to high clinical suspicion and confirmation with appropriate serology or antigen testing of either the peripheral blood or CNS. Rare is the report in the modern literature of a viral CNS infection diagnosed primarily on a histological biopsy as morbidity and mortality are nearly always increased with surgical intervention. In this handout, there are several long tables

listing the many viral diseases of the CNS, some of which are certainly considering new and emerging or re-emerging. However, one of the most challenging viral infections to definitively diagnose pre-mortem is Rabies, a topic on which we will expand a bit.



A current discussion of rabies virus incidence, prevalence and new understandings of biology and immune evasion will be presented.[1, 2]

Unlike viral infections which can be difficult to localize, bacterial infections can be greatly augmented by radiology and microbiological culture. When a bacterial abscess is present, the differential includes fungal and parasitic infections as well as non-infectious causes. Unlike viral infections, surgical drainage and/or biopsies are more common in order to drain abscesses and especially for antibiotic resistance testing in prolonged lesions. Although the pathologist may be able to give a gram staining pattern and a morphology reading, culture is required for definitive diagnosis and antibiotic testing. 16S rRNA PCR and sequencing can be performed on formalin fixed tissue when no culture is available (e.g., the CDC); however, this does not provide antibiotic susceptibility in most cases. Fungal infections can be evaluated using several peripheral blood markers (Galactomannan and Beta-1,3-glucan). Parasitic infections (with the

Bacterial CNS Infections

- Diagnosis is suspected clinical with supporting radiology with additional microbiological and/or CSF diagnostic tests including cytology
- Differential includes fungal and parasitic infections.
- Surgical procedures/biopsies are often required to drain true bacterial abscesses (especially anaerobic organisms) and are valuable on histology to exclude other causes.
- Microbiological culture from confirmed abscess material (diagnostic smear/frozen section) is required for definitive diagnosis.

exception of Toxoplasmosis) will usually have a clinical history of exposure; however, if patients are severely ill (i.e., coma) obtaining such a history may be difficult especially if family members are either not available or language is a barrier. Mycobacterial disease, especially disseminated tuberculosis, requires marked input from the neuropathologist with regards to the pattern of inflammation (granulomatous vs. neutrophilic), presence of AFB on special stains, etc. Let us further explore recent developments in the diagnosis of Mycobacterium tuberculosis in the CSF.

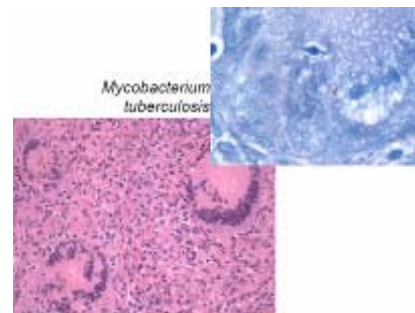
Bacterial CNS Infections Aseptic Meningitis Agents

- Partially-treated bacterial meningitis
- *Listeria monocytogenes*
- *Brucella* species
- *Rickettsia rickettsii*
- *Ehrlichia* species
- *Mycoplasma pneumoniae*
- *Borrelia burgdorferi*
- *Treponema pallidum*
- *Leptospira* species
- *Mycobacterium tuberculosis*
- *Nocardia* species

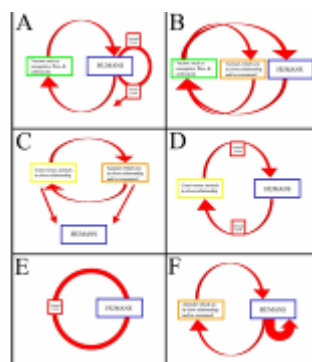
To begin, remember that aseptic or culture-negative meningitis can include a long list of organisms. Many of these organisms are aseptic because growth is not amenable to typical culture techniques and/or the specimen is not handled properly before arriving in microbiology. In some cases, however, growth may take an excessive amount of time (e.g., mycobacteria). Molecular techniques on both fresh tissue (if obtained) and CSF can be tremendously

helpful in ruling in these organisms (though not the opposite) and a role for traditional serology is still common for both CSF and peripheral blood. From the perspective of a neuropathologist, very few of these lesions are ever going to produce a brain biopsy (nor should they!) with the exception of *M. tuberculosis* and Nocardiosis—the former due to bulky granulomatous disease and the latter due to the propensity to form abscesses eventually. Both organisms have AFB staining patterns but can be easily distinguished by morphology and milieu.

A current discussion of detection of mycobacterial disease in the CNS will be presented[3, 4].



Parasitic Life Cycles:
How they get to the CNS



Parasitic disease is a catchall expression for any non-viral/non-bacterial/non-fungal disease of humans which includes some TRUE parasites but many opportunistic or incidental infections which can not truly be thought of as parasitic. For example, in the diagrams above are several schematics of general life cycles of parasites. Diagrams A, D, and E demonstrate what can be thought of as true parasitic relationships with

examples being malaria, tapeworms, and roundworms or entamoeba, respectively. In these cycles, humans are REQUIRED for the parasite to complete their lives and a significant number of patients infected with the organism are asymptomatic. B and C represent zoonotic diseases such as African Sleeping Sickness and Toxoplasmosis respectively in which humans are either incidental hosts or dead end hosts. In the former, disease is very severe in humans (with 100% mortality if not treated for African Sleeping Sickness) because humans are not commonly part of the life cycle. In the latter, the role of the human as a reservoir that must be “consumed” by another organisms such as a carnivore to complete the life cycle results in humans as a dead end host. These, although included in any textbook of parasitology, may not be considered true parasites by strict definitions. Diagram F is a special case, such as Taenia solium (the agent of cysticercosis), where humans can be part of a normal parasitic life cycle (i.e., humans have a tapeworm), but when the cycle is interrupted, humans change positions and become a dead end host. These diagrams are helpful in understanding why some infectious parasitic diseases present acutely while others may take months or years to manifest. For the sake of this discussion, we will now turn to helminthic parasitic diseases that lead to CNS complications.

Helminths come largely in three flavors in human infections. The nematodes, or roundworms, are largely isolated to the gastrointestinal tract and lymphatics and, with the exception of agents such as angiostrongylus (the most common cause of eosinophilic meningitis), do not cause CNS infections. The eyes are affected in Onchocerciasis (River Blindness) with the movement of microfilaria into the eyes with inflammatory response; however, this disease is a focus of international efforts to eliminate and reduce disease and so is hopefully on the decline. The cestodes (i.e., segmented flatworms or tapeworms) comprise two groups (see life cycles on previous slide) which include a) those that cause only intestinal tapeworms in humans and b) those that cause disseminated diseases in humans. Within the former group are the vast majority of tapeworms, which are of nutritional and public health concern but not major contributors to mortality. In the latter, we have Taenia solium (the pork tapeworm) and Echinococcus sp. (dog tapeworms) which lead to disseminated disease. The pork tapeworm disseminates when a human is exposed to the feces of a person with a tapeworm and ingests eggs or proglottids (as is the norm for the pig). Similarly, echinococcosis results from exposure to the feces of carnivores in the environment.

Helminthic CNS Infections

- **Nematodes**
 - Exceedingly Rare in the CNS
 - Mostly GI disease and lymphatics
- **Cestodes**
 - Mostly GI disease
 - CNS complications in life cycle disruptions
- **Trematodes**
 - Mostly vascular (adults) with tissue pathology complications (eggs)
 - Rare in CNS but a complication of chronic infection

Nematodes		
Luminal	Tissue Dwelling	Filarial Infections
<ul style="list-style-type: none"> • Oral exposure (ingestion) <ul style="list-style-type: none"> - Ascaris lumbricoide - Trichouris trichiura - Enterobius vermicularis - Capillaria philippinensis • Cutaneous exposure (skin passage) <ul style="list-style-type: none"> - Ancylostoma duodenale - Necator americanus - Strongyloides stercoralis 	<ul style="list-style-type: none"> • Zoonotic <ul style="list-style-type: none"> - Ancylostoma caninum - Ancylostoma braziliense - Toxocara canis, T. cati - Angiostrongylus - Trichostrongylus axei - Gastrostrongylus - Gastrostrongylus - Gastrostrongylus • Human <ul style="list-style-type: none"> - Onchocerca volvulus 	<ul style="list-style-type: none"> • Tropical <ul style="list-style-type: none"> - Wuchereria bancrofti - Brugia malayi - Onchocerca volvulus - Mansonella sp. - Loa loa • Zoonotic <ul style="list-style-type: none"> - Onchocerca volvulus - Onchocerca volvulus - North American Brugia

The nematodes comprise a large number of organisms as listed above though only a few ever involve the CNS. The four highlighted in bold (Ascaris, Trichostrongylus, and the two hookworm species) combined infect approximately 3.5 billion people world wide.

Virus (Family)	Viral Structure	Transmission	Mortality Rate	Specific Clinical Patterns	Sequelae	Season
Herpes simplex virus (herpesvirus)	*ds DNA	Unknown	70% if untreated	Rare forms: subacute, psychiatric, opercular, recurrent meningitis HSV-1: brainstem HSV-2: myelitis	Common	All year
Varicella-zoster (herpesvirus)	*ds DNA	Direct contact (air), highly contagious	Variable; low in children	Rash, encephalitis in 0.1-0.2% children with chickenpox; cerebellar ataxia (cerebellitis)	Adults worse; cerebellitis good	Late winter, spring
Influenza virus (orthomyxovirus)	*ss RNA	Direct contact (air), highly contagious	Unknown	Reversible frontal syndrome in children; Guillain-Barré, myelitis	Parkinsonism (encephalitis lethargica)	Usually winter
Enteroviruses (picornavirus)	*ss RNA	Fecal-oral route	Low; high for enterovirus 71	Herpangina; hand, foot, mouth disease; enterovirus 71 causes rhombencephalitis	Mild, except for enterovirus 71	Summer, fall; tropics: no season
Rabies (rhabdovirus)	*ss RNA	Dog, wild animals (eg, fox, wolf, skunk)	Virtually 100%	Paresthesias; confusion, spasms, hydrophobia; brainstem features	Mortality rate virtually 100%	All year

* Abbreviations: ds - Double strand; ss - Single strand

Virus (Family)	Viral Structure	Transmission	Distribution	Mortality Rate	Specific Clinical Patterns	Sequelae	Season
Lymphocytic choriomeningitis virus (arenavirus)	*ss RNA	Rodents	Europe, Americas, Australia, Japan	Low (<1%)	Progressive fever and myalgia; orchitis; aseptic meningitis; leukopenia, thrombocytopenia	Rare	More in winter
Lassa fever (arenavirus)	*ss RNA	Rodents	Africa	15%	Multisystem disease; proteinuria	Deafness (one third)	All year
Mumps (paramyxovirus)	*ss RNA	Direct contact (air), highly contagious	Worldwide	Low	Parotitis, pancreatitis, orchitis, aseptic meningitis	Frequent sequelae	Winter and spring
Measles (paramyxovirus)	*ss RNA	Direct contact (air), highly contagious		10%	Characteristic rash; frequent EEG changes; myelitis	Frequent: mental retardation, seizures, *SSPE	Winter and spring
Nipah virus (paramyxovirus)	*ss RNA	Pigs; bats	Malaysia (Asia)	40%	Brainstem/cerebellar signs; segmental myoclonus, dysautonomia	*SSPE-like syndrome?	All year

*Abbreviations: ds - Double strand; ss - Single strand; SSPE - Subacute sclerosing panencephalitis

Virus (Family)	Vector	Reservoir	Dist.	Mortality Rate	Specific Clinical Patterns	Sequelae	Season
Eastern equine (alphavirus)	<i>Aedes sollicitans</i>	Birds	Eastern and Gulf US, Caribbean	35 %	Severe, rapid progression	Common, especially in children	June to October
Western equine (alphavirus)	<i>Culex tarsalis</i>	Birds	Western US	10 %	Classic encephalitis	Moderate in infants; low in others	July to October
Venezuelan encephalitis (alphavirus)	Mosquito species	Horses, small mammals	South/Central America	~ 0.4 %	Low rate (4%) of CNS involvement	Mild	Rainy season
St. Louis (flavivirus)	<i>Culex pipiens</i> , <i>C. tarsalis</i>	Birds	Widespread in US	2 % young people; 20 % elderly people	*SIADH	More in elderly people	August to October
Japanese B encephalitis (flavivirus)	<i>Culex taeniorhynchus</i>	Birds	Asia	33 % (50 % in elderly people)	Extrapyramidal features	50 % neuro-psychiatric; parkinsonism	Summer
West Nile (flavivirus)	<i>Culex</i> , <i>Aedes</i> species	Birds	Africa, Asia, Europe, USA	In US: 12 % (elderly people only)	Motor/brainstem involvement	Usually not prominent	Summer
Far East tick-borne encephalitis (flavivirus)	<i>Ixodes persulcatus</i> (tick)	Small mammals, birds	Former eastern Russia	20 %	Epilepsia partialis continua	Frequent; residual weakness	Spring-early summer
Central European tick-borne encephalitis (flavivirus)	<i>Ixodes ricinus</i> (tick)	Small mammals, birds	Central Europe	Less common than in Far East	Limb-girdle paralysis (spine/medula)	Less common than in Far East	April to October
Powassan (flavivirus)	<i>Ixodes cookei</i> (tick)	Small mammals, birds	Canada, northern US	High	Severe encephalitis	Common (50%)	May to December
Dengue fever (flavivirus)	<i>Aedes</i> species	Mosquitoes	Tropics	Low, except hemorrhagic	Flulike syndrome; rare CNS involvement	Mild, except for hemorrhagic	Rainy season
La Crosse (bunyavirus)	<i>Aedes triseriatus</i>	Small mammals	Central US	Low (<1%)	Mild, primarily in children	Mild; seizures	Summer
Colorado tick fever (orbivirus)	<i>Dermacentor andersoni</i> (tick)	Small mammals	US, Rocky Mountains area	Low		Mild	

*Abbreviations: SIADH – Syndrome of inappropriate antidiuretic hormone secretion

Summary and Conclusions

- An understanding of Rabies biology is pointing towards new pathways for treatment of the deadly disease which has had a surprising increase in incidence in the last decade.
- Diagnosis of disseminated tuberculosis prior to biopsy is still difficult making tissue samples vital for the moment; however, new markers should greatly increase the accuracy of this diagnosis.
- “Chronic” silent diseases can re-emerge as advance treatments with immunosuppression are more commonly used in traveling populations.
- As the global population is increasingly linked by rapid travel, new economic vectors, and improved healthcare, the incidence and prevalence of previously restricted tropical diseases will increase in North America

See the following articles for the discussion of rabies, tuberculosis, Strongyloides and cysticercosis.

1. Roy A Fau - Hooper, D.C. and D.C. Hooper, *Immune evasion by rabies viruses through the maintenance of blood-brain barrier integrity.* (1538-2443 (Electronic)).
2. Jackson Ac Fau - Randle, E., et al., *Neuronal apoptosis does not play an important role in human rabies encephalitis.* (1538-2443 (Electronic)).
3. Christie Lj Fau - Loeffler, A.M., et al., *Diagnostic challenges of central nervous system tuberculosis.* (1080-6059 (Electronic)).
4. Be Na Fau - Lamichhane, G., et al., *Murine model to study the invasion and survival of Mycobacterium tuberculosis in the central nervous system.* (0022-1899 (Print)).
5. Nishimura K Fau - Hung, T. and T. Hung, *Current views on geographic distribution and modes of infection of neurohelminthic diseases.* (0022-510X (Print)).
6. Walker Md Fau - Zunt, J.R. and J.R. Zunt, *Neuroparasitic infections: nematodes.* (0271-8235 (Print)).
7. Patil S Fau - Robinson, P., et al., *Proinflammatory cytokines in granulomas associated with murine cysticercosis are not the cause of seizures.* (0022-3395 (Print)).
8. Morales-Montor J Fau - Escobedo, G., et al., *The neuroimmunoendocrine network in the complex host-parasite relationship during murine cysticercosis.* (1873-4294 (Electronic)).