



# NEUROLOGY CONFERENCE 2 CNS INFECTIONS IN SSA

PROF E BADOE MRCP(UK) FRCPCH FGCP

HEAD OF NEUROLOGY SERVICES, DEPT OF CHILD HEALTH,

5<sup>TH</sup> SEPTEMBER, 2019

EAN REGIONAL TEACHING COURSE , SUB SAHARAN AFRICA



# DEPT OF CHILD HEALTH



# IMPACT AND EPIDEMIOLOGY OF VIRAL, PARASITIC AND BACTERIAL INFECTIONS IN SSA

Infections of the CNS are  
devastating with a high mortality  
and morbidity in SSA





# IMPACT AND EPIDEMIOLOGY OF VIRAL, PARASITIC AND BACTERIAL INFECTIONS IN SSA

- Neglected tropical disease (NTDs) affect the poorer countries in SSA.
- Polio remains active and the non polio enteroviruses. Adenovirus are rife.
- Rarer conditions like the West Nile virus, chikungunya, zika and ebola predominantly found in SSA

# POLIO

- Recent headlines in Ghana – endgame in sight?

In case of the reply the number and the date of this letter should be quoted.

My Ref. No. GHS/DGS/1.5

Your Ref. No. ....



GHANA HEALTH SERVICE  
PRIVATE MAIL BAG  
MINISTRIES  
ACCRA. GHANA.

Tel: 685372  
Fax: 666808

August 23, 2019

## PRESS RELEASE

### POLIO OUTBREAK IN CHEREPONI DISTRICT, NORTHERN REGION, GHANA; AUGUST 2019

The Ministry of Health / Ghana Health Service has received report of confirmed Poliomyelitis from the National Polio Laboratory, in the sample from a two (2)-year eight (8) month old girl with Acute Flaccid Paralysis (AFP) from Andonyama in Chereponi sub-district of Chereponi district in the Northern Region.

The child was seen at Chereponi District Hospital on the 27 July with sudden onset of weakness in both lower limbs, stool samples were taken as part of routine polio surveillance on 27th July, 2019 and sent to the National Polio Laboratory at Noguchi Memorial Institute for Medical Research for laboratory investigations and the sample tested positive as per result received on 17<sup>th</sup> August, 2019.



# POLIO

- Nigeria- hopes to declare a polio free status next year after 3 years without a case
- Highly infectious enterovirus of antigenic types 1, 2, and 3.



# POLIO

- In children wild virus may invade CNS causing an aseptic meningitis (non paralytic polio)
- Pathological lesions involve the anterior horn cells, motor and sensory nuclei of the medulla, reticular formation, cerebellar vermis
- Common spinal poliomyelitis characterized by asymmetrical flaccid paralysis involving the legs, arms or trunk with absent tendon reflexes
- Urinary retention is present in 20-30% of cases





# ENTEROVIRUSES

- Important potential cause of neurologic disease in African children.
- Enter host via gastrointestinal tract, replicate and can lead to an infection of the CNS
- Infections typically occur during tropical rainy season. Lowest during harmattan. Risk of infection linked to poor hygiene, poor sanitation and overcrowding



# ENTEROVIRUSES

- Signs:
  - Diarrhea
  - abdominal discomfort
  - maculo-papular rash
- Children present with acute encephalitic features



# ENTEROVIRUSES

- Enterovirus 71 causes acute flaccid paralysis resembling guillan barre syndrome
- Recent studies suggest it can now be detected in blood using PCR techniques. *Lafolie J et al. Lancet infect dis 2018.*
  - Currently RT-PCR on CSF samples for detection.



# ENTEROVIRUSES

- Management:
  - Supportive care.
  - Plecornil prevents virus from attaching to cellular receptors and releasing viral DNA. Benefit in certain cases



# RABIES

- Prevalence in SSA second globally to Asia with around 24,000 deaths each year
- Virus in infected mammals like dogs, cats.
- In Africa, mainly through dog bites. Lyssa virus after Greek spirit of madness and frenzy

# RABIES

- Incubation period of 20 to 60 days
- Signs:
  - Chills
  - Fever
  - Headache
  - Sore throat
  - Abdominal pain
- Pain or itching at the site of inoculation common



# RABIES

- Virus replicates in skin and reaches CNS by retrograde axonal transport via peripheral nerves
- Furious “ rabies:
  - Hydrophobia
  - violent episodes of hyperexcitability and lucidity followed by coma and death



# RABIES

- Copious flushing of wound with saline solution or cetrimide plus chlorhexidine solution
- Infiltrate wound with rabies immunoglobulin 10 IU/kg .
- Update tetanus immunization.
- Commence antirabies vaccine and immunoglobulin depending on condition of animal at time after attack.





# RABIES

- Ethiopia has one of the highest rates in Africa
- Global strategic plan to eliminate rabies by 2030
- Africa lacks an effective rabies control program
- Lacks information about actual cases of rabies
- Unwillingness to bring dogs for vaccination
- Many dogs are ownerless”
- Lack of surveillance and diagnostic capacity for rabies detection and cost of dog vaccination campaigns. *Lembo T plos negl trop dis 2010*



# WEST NILE VIRUS (ARTHROPOD –BORNE ENCEPHALITIS)

- Mosquito born RNA virus (flavivirus and broadly arboviruses)
- Endemic throughout Africa
- Serologic evidence of human exposure in Ghana, Gabon, South Africa and Cameroon. Wang W, sarkodie F, danso K et al. *Viral immunol* 2009



# WEST NILE VIRUS (WNV)

- WNV maintained in nature in a cycle between birds and mosquitoes and culex species plays largest role in transmission
- Humans and horses are incidental hosts
- Approximately 5% of patients with symptomatic infection develop neurologic disease



# WNV

- **Diagnosis:**
  - Diagnosis is by detecting IGM antibody in CSF, serum
  - Detecting virus in nucleic acid in CSF blood
- **Treatment:**
  - It is supportive
- **Prevention:**
  - focus on surveillance, elimination of mosquito breeding sites and adult mosquito management using pesticides.



# WNV

- Treatment:
  - It is supportive
- Prevention:
  - focus on surveillance, elimination of mosquito breeding sites and adult mosquito management using pesticides.



# COMMONEST VIRUS IN SSA?

- Important paper published by Mallewa M, Valleyly P et al in lancet global health vol 2 2013.
- Most commonly detected virus in the CNS was **adenovirus** followed by mumps, human herpes virus 6, and rabies virus.



# HERPES SIMPLEX ENCEPHALITIS (HSE)

- Presents with encephalopathy(altered mental state), deteriorating level of consciousness, focal seizures, focal neurological abnormalities
- Neonatal HSE commoner. Skin lesions may be present



# HERPES SIMPLEX ENCEPHALITIS (HSE)

## Diagnosis:

- Best neuroimaging is MRI
- EEG required?

## • Management:

- High dose iv aciclovir is most effective when started early



# TEMPORAL LOBE AFFECTED IN HERPES





# PARASITIC CNS INFECTIONS

- **Cerebral malaria (CM)**
  - 90% of deaths occur in Africa (*WHO 2008*)
- Cases falling in Africa.
  - Prevention strategies appear to be working



# CM

- Vascular level occlusion leads to microhemorrhages and reduced perfusion
- Altered transmembrane transport, hypoxia, cell swelling, anaerobic glycolysis, lactic acidosis and cell death
- Changes lead to endothelial damage with increased blood brain barrier permeability
- Changes lead to brain swelling and raised ICP reducing cerebral blood flow



# CM

- Diagnosis based on unrousable coma in the presence of *P. falciparum* parasitaemia in the peripheral blood
- Recently important to include an assessment for malaria retinopathy in the diagnosis of CM *Beare NA, Lewallen S, Taylor T. Redefining cerebral malaria by including malaria retinopathy. Future microbiol mar; 6(3):349-55*
- Primary treatment is with parenteral quinine or artemisinin derivatives. Artemisinin have a better safety profile, fewer serious side effects



# NEUROCYSTICERCOSIS

- Very common parasite in the CNS in SSA
- Important cause of seizures in children in endemic countries
- Pig production widespread in Cote Ivoire and Togo
- Nigeria has 5 million pigs (biggest in West Africa)



# NEUROCYSTICERCOSIS

- Infection by *Taenia solium*
- Neurocysticercosis reflects the death of larvae within the brain and spinal cord
- Presents with headache, seizures, focal deficits, visual dysfunction, behavioural changes and papilledema



# NEUROCYSTICERCOSIS

- **Diagnosis-**
  - MRI and CT show circular or ring enhancing lesions typically with adjacent oedema.
  - CSF- eosinophilic lymphocytosis and elevated protein.
  - Enzyme linked immunoelectrotransfer blot eitb assay. Sensitivity 98% specificity 100%.
- Treatment with albendazole for 7 days. Dexamethasone or prednisolone given before or concurrently to minimize symptoms associated with parasite death





# HUMAN AFRICAN TRYPANOSOMIASIS



*Trypanosoma brucei gambiense* – West African trypanosomiasis



*Trypanosoma brucei rhodesiense* – East African disease (Tanzania, Uganda, Malawi and Zambia)  
95% of cases



Currently 50,000-70,000 cases in Africa



10,000 new cases annually (WHO 2016)



Transmitted by bite of tse tse fly



# TRYPANOSOMIASIS

- Initial multiplication of parasites at infection site followed by hemolympathic stage
- Waves of parasitemia
- Invasion of nervous system next causing leukoencephalitis (meningoencephalitic stage)
- West African disease indolent
- East African disease more acute progression



# TRYPANOSOMIASIS

- East african disease can present with
  - Headache
  - personality changes
  - psychiatric disorders
- Characteristic sleep disturbance



# TRYPANOSOMIASIS

## Diagnosis:

- direct observation of intracellular trypomastigotes in serum or CSF.
- Neuroimaging typically show more than one ring enhancing lesions involving both grey and white matter
- Stage 1 drugs- suramin and pentamidine
- Stage 2 (encephalitic stage) arsenic compounds (melarsoprol. ) Or dl-a – difluoromethylornithine(dfmo)



# TOXOPLASMOSIS

- Widely distributed causing infection in all warm blooded animals including humans
- Parasitic infection caused the protozoan *Toxoplasma gondii*
- In Africa childhood toxoplasmosis through congenital infections
- A study suggests *T gondii* widespread in Mali and elsewhere in West Africa in both urban and rural areas. *Ouologuem DT djimde AA et al. Toxoplasma gondii seroprevalence in mali. J parasito apr;99(2): 371-4*



# TOXOPLASMOSIS

- Children with HIV-toxoplasmosis due to reactivation of latent infection
- One third of HIV infected people with serum anti-toxoplasmosis IgG antibodies develop toxoplasma encephalitis *luft BJ, remington JS. AIDS commentary. Toxoplasmic encephalitis. J infect dis 1988 157(1): 1-6*



# TOXOPLASMOSIS

- Incidence of toxoplasma encephalitis reduced among HIV infected people receiving trimethoprim-sulphamethoxazole or dapsone/pyrimethamine therapy as prophylaxis against pneumocystis carinii pneumonia
- Congenital toxoplasmosis occurs when maternal infection occurs late in pregnancy
- Leads to ocular disease (chorioretinitis or congenital neurologic deficits or learning disabilities)



# TOXOPLASMOSIS

- Learning difficulties do occur. Advancing age of child due to recrudescence of bradyzoite cysts established in infant *holland GN. Ocular toxoplasmosis. The influence of patients age. Mem inst oswaldo cruz 2009 mar;104(2):351-7*
- In immunocompromised children/adults clinical manifestations of CNS toxoplasmosis include headache, altered mental status, focal neurologic deficits, ataxia, cranial nerve palsies *Patchell RA. Neurological complications of organ transplantation ann neurol 1994 nov;36(5):688-703*



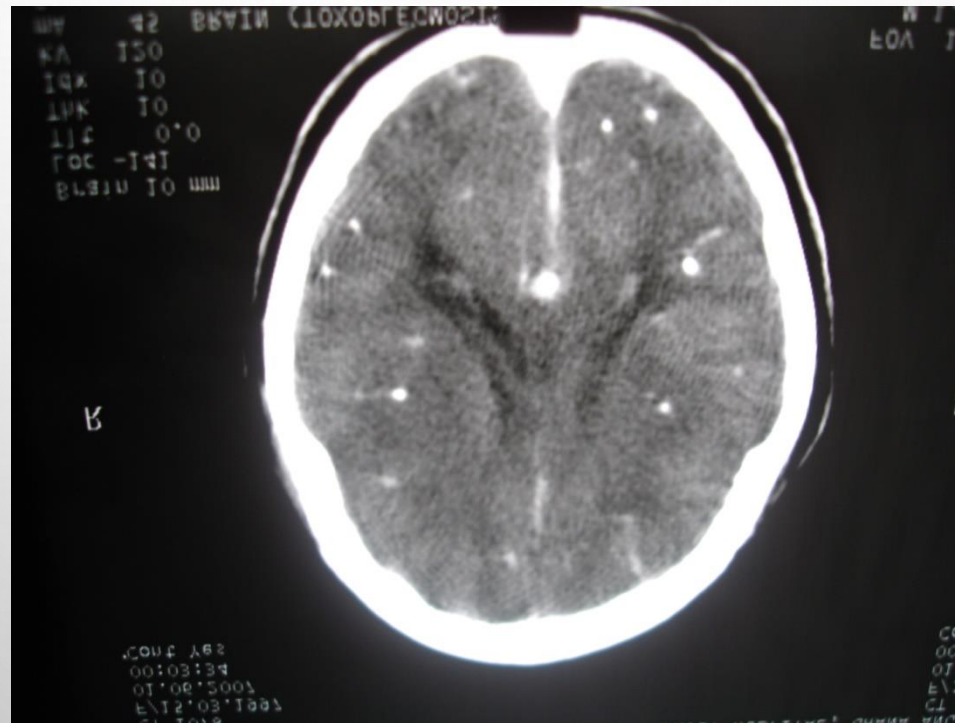


# TOXOPLASMOSIS

## Diagnosis:

- Anti-t gondii antibodies by ELISA both sensitive and specific
- Multiple ring enhancing lesions in the basal ganglia or cerebrum on CT or MRI in the presence of anti-toxoplasmos igg antibodies suggest presence of CNS toxoplasmosis
- Drug treatment of CNS toxoplasmosis includes pyrimethamine, sulfadiazine and folinic acid

# IMAGE OF TOXOPLASMOSIS





# SCHISTOSOMIASIS (BILHARZIAS)

- Second only to malaria as the most devastating parasitic disease.
- Tourists at risk from eco tourism
- Ghana an endemic area especially after construction of the big Akosombo dam in 1965.
  - First disease prevalence study in Ghana surveys in 1963 estimated 15-20% of people in Ghana were infected with schistosomiasis in their lifetime!



# SCHISTOSOMIASIS

- Neuroschistosomiasis is the most severe clinical form of the infection.
- In Ghana *S mansoni* and *S haematobium* predominate.
- Neurological complications from egg deposition and follows migration of adult worms to the brain or spinal cord
- Followed by granuloma formation surrounding thousands of eggs deposited and the hallmark of neuroschistosomiasis *carod –artal FJ. Neurological complications of schistosoma infection. Trans R soc trop med hyg 2008*



# SCHISTOSOMIASIS

- Neuro signs- RICP, myelopathy, radiculopathy
- Headache, visual disturbance, delirium , seizures, ataxia and encephalopathy
- Spinal cord involvement –back pain, limb pain, muscle weakness, sensory loss, bladder dysfunction
- Acute transverse myelitis and sub acute myeloradiculopathy of lumbo sacral region probably most commonly reported neurological manifestation of *S mansoni* and *S haematobium*



# SCHISTOSOMIASIS

- Cortex involvement, subcortical white matter/basal ganglia or internal capsule leads to acute encephalitis in *S japonicum carod-artal FJ*.  
*Neurological complications of schistosoma infection. Trans R soc trop med hyg.2008*
- Diagnosis:
  - Postive diagnostic finding of eggs in stool plus neuroimaging and above listed presentation makes neuroschistosomiasis likely
  - Definitive diagnosis by biopsy and histopathological study when granulomas exist



# SCHISTOSOMIASIS

## Management:

- Praziquantel effective for all species and curative in 60-90% of cases. If not effective oxamniquine can be used.
- Artemether can be effective against immature migrating larvae (schistosomula)



# TUBERCULOSIS/DEVELOPMENTS

- TB responsible for more deaths than any other infection.
- Pan ACEA consortium identifying ways to accelerate TB drug development
- Platform for TB drug trials across Africa
- High dose rifampicin has shown great promise as part of regime to shorten the TB treatment regime





# TUBERCULOSIS

- 4% of people with HIV in SSA are infected with TB.
- One in five such patients experience a severe inflammatory reaction known as TB-IRIS. Immune system as it recovers from treatment responds too vigorously to the TB infection.



# TUBERCULOSIS

- New BCG vaccine engineered based on *M tuberculosis* to eliminate genes central to disease while maintaining those lost in BCG traditional vaccine that provoke a strong immune response.
- Currently we know BCG vaccine less effective in the older age group
- Spentini F et al published a paper on the safety of human immunisation with a live attenuated mycobacterium tuberculosis vaccine. *MTBVAC A randomised double blind controlled trial phase 1. Lancet respir med 2015(12):957-62*



# TUBERCULOSIS

- Large scale trials going on in Senegal and Madagascar. Better protection for newborns on the horizon and ? prevention of TB meningitis?
- First live attenuated vaccine to reach clinical trials stage showing similar safety to BCG
- WHO recommends Xpert MTB/RIF as the new molecular diagnostic test for TB. Both sensitive and specific.



# TUBERCULOSIS

- New dipstick test on the horizon
- LAM –TB test detects lipoarabinomannan) a. A molecule derived from mycobacterium TB in the urine. LAM antigen a lipopolysaccharide derived from active TB cells or degenerating cells and occurs only in people with active TB
- Adding a dipstick test in trials shown to reduce risk of death by 17% at 8 weeks. Leads to better detection of TB than from sputum.
- A policy statement now from who on the use of LAM TB test for people living with HIV and active TB as a potential point of care test.



# TUBERCULOSIS

- TAM –TB assay – a rapid blood test that detects changes in the number of particular immune cells showing good specificity and excellent sensitivity. *Portevin D et al. Assessment of the novel T cell activation marker tuberculosis assay for diagnosis of active tuberculosis in children.- A prospective proof of concept study. Lancet infect dis. 2014;70(4) 392-9*
- Sputum independent
- Developed in Tanzania at the national institute for medical research, Mbeya.
- Diagnoses active TB in children



# TUBERCULOSIS

- First immunodiagnostic tool to detect active TB in children with sensitivity similar to culture
- Measures CD 27 phenotype of CD4 T cell.



# HIV

- More than 3 million HIV infected children live in Africa
- One in five HIV related deaths in Africa attributed to opportunistic fungal infection.
- Cryptococcal meningitis responsible for 500,000 deaths in SSA. *Molloy sf et al. Cryptococcal meningitis . a neglected tropical disease? Plos neg trop dis 2017;11;(6)*
- Improving management of meningitis in HIV infected individuals new dipstick diagnostic test for cryptococcal infection developed



# HIV

- Craglfa test -effective in resource limited setting like SSA. (Cryptococcal antigen lateral flow assay.
- Test provides an indication of the severity of infection and need for more treatment even when asymptomatic and revolutionizing cryptococcal antigen testing.
- A dipstick immunochromatographic assay
- Akin to home pregnancy test. No need for sophisticated lab to do tests lacking in SSA. Meets WHO standards





# HIV

- New mosaic vaccine being developed by tomas hank at the university of oxford.
- Second generation vaccine



# SUMMARY

- A not exhaustive but important CNS infections peculiar to SSA has been presented.
- Some are well known having existed since antiquity like rabies.
- Basic presentation of the diseases in ssa presented with short reviews of emerging viral infections in ssa like west Nile virus.
- New developments in hiv, tb detection presented.



# CONCLUSION

- Overview of the impact of CNS diseases shows that serious infections still exist on the continent.
- Immunization cover improving in SSA and polio, haemophilus type b meningitis, mumps meningoencephalitis, rubella embryopathy and subacute sclerosing encephalopathy are not routinely reported . A lot more not prevented by immunization as shown
- Virus infections in particular induce a wide spectrum of disease from benign to lethal situations,





# REFERENCES / ACKNOWLEDGEMENTS

- Mallewa M. Wilmsurst J. Overview of the effect and epidemiology of parasitic Central nervous system infections in African children. Semin Pediatr Neurol 2014 21(1)19-25
- Badoe E, Wilmshurst J. Overview of the effect and epidemiology of viral central nervous system infections in African children. Semin Pediatr Neurol 2014 21 (1) 26.9
- European Developing countries clinical trials partnership (EDCTP).9<sup>th</sup> forum website.