Introduction

• What is immunosuppression?
  – Congenital; acquired; iatrogenic
  – Caveats: adult physician; not an immunologist; will focus on CNS

• What neurological presentations?
  – Infectious vs non-infectious

• Case examples

• Immune reconstitution

• Conclusions
What is Immunosuppression?

- Impaired immune response due to congenital, acquired or iatrogenic causes.
  - Impairment of cell-mediated immunity
    - Inability to fight intracellular organisms e.g. listeria; MTB
  - Impairment of humoral immunity
    - Hypogammaglobulinaemic patients: nb enterovirus
  - Impairment of innate immunity
    - Splenectomised patients & encapsulated organisms e.g. pneumococcus
What is Immunosuppression?

• Acquired immunosuppression
  – Systemic illness
    • Diabetes mellitus; chronic alcoholism; renal or hepatic failure; autoimmune disorders (e.g. SLE or sarcoid)
  – HIV/AIDS (other infections e.g. measles)
  – Malignancy
  – Haematological
    • Bone marrow failure; splenectomy; SSD; myeloma
  – Age (old & young)
  – Pregnancy
  – Iatrogenic

• Congenital e.g. idiopathic CD4 lymphopenia
Iatrogenic Immunosuppression

• Drugs
  – Corticosteroids; steroid-sparing agents; biologics
  – Risks greater when on multiple agents

• Ionising Radiation
# Immunosuppressive Drugs

<table>
<thead>
<tr>
<th>Drug or Drug family</th>
<th>Mechanism of Action</th>
<th>Infection Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Suppress innate &amp; adaptive immune system</td>
<td>Bacterial; mycobacterial; fungal &amp; viral</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Dihydrofolate reductase inhibitor</td>
<td>Increased risk of UTIs &amp;c little evidence of opportunistic infections</td>
</tr>
<tr>
<td>Cyclophosphamide &amp; other alkylating agents</td>
<td>T &amp; B-cell suppressive effects</td>
<td>Bacterial; mycobacterial; fungal &amp; viral</td>
</tr>
<tr>
<td>TNF alpha inhibitors</td>
<td>Inhibit granuloma formulation &amp; maintenance</td>
<td>Granulomatous infection (TB; fungal; toxoplasmosis). Increased risk of extrapulmonary TB</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Depletion of CD20 cells</td>
<td>PML</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Alpha-4 integrin inhibitor</td>
<td>PML (4.2/1000)</td>
</tr>
<tr>
<td>Fingolomod</td>
<td>Sphingosine 1-receptor modulator; inhibits lymphocyte egress from LN</td>
<td>HSV/VZV; PML; cryptococcus</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Shifts TH1 to TH2; lymphopenia</td>
<td>PML</td>
</tr>
</tbody>
</table>
Non-Infectious Neurological Presentations of Immunosuppression

- Malignancy
  - E.g. Primary CNS lymphoma; melanoma
- Graft versus host disease e.g chronic myositis
- Posterior reversible encephalopathy syndrome (usually drug-related – tacrolimus/cyclosporine)
- Post transplant lymphoproliferative disease
- Drug-induced autoimmunity (demyelination triggered by anti TNF alpha drugs; hypophysitis with checkpoint inhibitors).
- Other drug neurotoxicities e.g. toxic neuropathy, cerebellar toxicity, seizures, myelopathy
Posterior reversible encephalopathy syndrome (PRES) can have many MRI variations, as shown in these fluid-attenuated inversion recovery (FLAIR) MRI sequences.

A, The typical pattern seen in PRES is hyperintensity in the occipital lobes.

B, More widespread PRES, with involvement of more anterior cerebral areas.

C, Laminar necrosis after resolution of the acute PRES episode.

D, An extensive brainstem abnormality producing hydrocephalus caused by PRES and fully reversible.
What are the differences in infection presentation between an immunocompetent and immunosuppressed person?

• Symptoms
  – Often subacute and lacking prominent inflammatory response.

• Organisms
  – Atypical microbes that otherwise might be considered commensals e.g. atypical mycobacteria
  – Atypical presentations of commonly pathogenic infections e.g. brain stem presentations of HSV encephalitis in HIV/AIDS.
Diagnosis of Acute Neurological Infection

• The neurological formulation:
  • Anatomy
  • Pathogenetic mechanism
  • Aetiology

• The ID mantra:
  • Why did this person?
  • From this place?
  • At this time, get this disease?

Solid Organ Transplant

- **Think about the organ donor**
  - West Nile Virus (USA)
  - Rabies (USA)
  - Halicephalobus (2013)
    - Nematode – x2 UK transplant cases*
  - CMV & EBV status of donor / organ

Principles of HIV Neurology

• **Time Locking**
  – Relationship to CD4 cell count

• **Parallel Tracking**
  – Involvement of multiple parts of the nervous system

• **Layering**
  – Different pathologies superimposed

• **Unmasking**
  – Second pathology dominated by subacute first pathologies symptoms e.g. HIVE & Cryptococcus

Brew (2001) HIV Neurology *OUP*
# Neurological Complications of HIV

## Box 7 Neurological complications of HIV

<table>
<thead>
<tr>
<th>CD4 T cell count/μl</th>
<th>Opportunistic infection</th>
<th>Direct HIV related neurological complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500</td>
<td></td>
<td>▶ Aseptic meningitis/meningoencephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Guillain–Barré syndrome</td>
</tr>
<tr>
<td>200–500</td>
<td>▶ Tuberculous meningitis</td>
<td>▶ Chronic inflammatory demyelinating polyneuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Mononeuritis multiplex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ HIV driven distal symmetrical axonal sensory polyneuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Antiretroviral drug related toxic distal symmetrical axonal sensory polyneuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ HIV headache</td>
</tr>
<tr>
<td>50–200</td>
<td>▶ Cryptococcal meningitis</td>
<td>▶ Vacuolar myelopathy</td>
</tr>
<tr>
<td></td>
<td>▶ Cerebral toxoplasmosis</td>
<td>▶ Autonomic neuropathy</td>
</tr>
<tr>
<td></td>
<td>▶ Progressive multifocal leucoencephalopathy</td>
<td>▶ HIV dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Primary CNS lymphoma (Epstein–Barr virus related)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>▶ CMV polyradiculopathy/mononeuritis multiplex/encephalitis</td>
<td></td>
</tr>
</tbody>
</table>

All complications listed at higher CD4 cell counts can occur at lower CD4 cell counts. Progressive multifocal leucoencephalopathy can occur at higher CD4 cell counts.

Mass Lesion in HIV

Management of HIV patients with focal neurology & CD4 cell count <200 cells/μL.

- G6PDH deficiency & sulphadiazine
- SPECT scans

Differentiating CNS Toxoplasmosis from PCNSL in HIV

<table>
<thead>
<tr>
<th>CNS Toxoplasmosis</th>
<th>PCNSL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia and corticomedullary junction</td>
<td>Sub ependymal spread</td>
</tr>
<tr>
<td>Multifocal</td>
<td>Solitary</td>
</tr>
<tr>
<td>Nodular or ring enhancing</td>
<td>Solid enhancement; may be ring</td>
</tr>
<tr>
<td>MRS – increased lactate</td>
<td>MRS – increased choline</td>
</tr>
<tr>
<td>PCR – low sensitivity; most seropositive</td>
<td>PCR – often high cope load of EBV</td>
</tr>
</tbody>
</table>
## Viral Infections in Immunocompromised

<table>
<thead>
<tr>
<th>Virus</th>
<th>Syndrome</th>
<th>Risk Factor</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1</td>
<td>Limbic encephalitis</td>
<td>Multiple; nb radiation</td>
<td>CSF PCR</td>
</tr>
<tr>
<td><strong>VZV</strong></td>
<td>Shingles (sine herpete); vasculopathy; segmental motor weakness; cranial neuropathies; retinitis; meningitis; myelitis.</td>
<td>GvHD; calcineurin inhibitors; corticosteroids</td>
<td>CSF PCR; CSF antibody studies</td>
</tr>
<tr>
<td>CMV</td>
<td>Encephalitis; retinitis; myelitis</td>
<td>T-cell depletion; solid organ transplants: donot organ positive</td>
<td>Ependymal enhancement on MRI; CSF PCR</td>
</tr>
<tr>
<td>EBV</td>
<td>Meningoencephalitis; post transplant lymphoproliferative disorder</td>
<td>Solid organ transplant: donor organ positive</td>
<td>CSF PCR</td>
</tr>
<tr>
<td>HHV-6</td>
<td>Limbic encephalitis; myelitis</td>
<td>Cord blood cell source; SIADH</td>
<td>CSF PCR</td>
</tr>
<tr>
<td>JCV</td>
<td>PML; granular cell neuronopathy</td>
<td>Lymphopenemia; MS drugs</td>
<td>CSF PCR</td>
</tr>
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</table>
MRI in Progressive Multifocal Leuкоencephalopathy

Pulmonary sarcoid & focal seizures
Case 1 MRI head scans

Axial MR images: T2 and T1 with gadolinium
Case 1 Further tests

- **Pulmonary and CNS TB**
- Pulmonary & CNS Cryptococcal infection
- Invasive aspergillosis
Long term fungal cultures

- Dematiaceous fungi isolated
- Aspergillus PCR test: Negative
- Pan fungal PCR test: POSITIVE
- PCR sequence identification: 

*Cladophialophora bantiana*

- Amphotericin 1.0 Sensitive
- Itraconazole 0.06 Sensitive
- Voriconazole 0.06 Sensitive
- Posaconazole 0.06 Sensitive
- Flucytosine 2 Sensitive
CNS Fungi

- Aspergillus
  - Necrotising Vasculitis

- Candida
  - Microabsses
  - Fundoscopy
CNS Fungi

- CSF – lymphocytosis, high pressure/protein, low glucose
- Serum beta glucan
  - Sensitivity ~70%
- Serum Galactomannan
  - Up to 95% sensitivity for *Aspergillus*
- 18S rRNA
  - *CSF, serum, sputum*

Alcoholic Traveller

MRI head scan - axial T1 with gadolinium
Aerobic bottle from 2 sets of cultures
Gram negative rods
Melioidosis

Microbe: *Burkholderia pseudomallei*

Pulmonary involvement commonest

CNS melioid

*Rare*

Mortality up to 25% ¹

Risk factors

Diabetes mellitus, Immunosuppression, *Alcohol excess* ²

Aerobic bottle from 2 sets of cultures

Gram negative rods

**Listeria monocytogenes**

- Intracellular pathogen; invasive listeriosis; meningitis rhombencephalitis
- Motile gram positive rods
- Empirical treatment in >60 yrs presenting with meningitis
- Poor response to cephalosporins
- Blood cultures; CSF cultures and CSF PCR

Immune Reconstitution Inflammatory Syndrome (IRIS)

• Definition:
  “a paradoxical deterioration in clinical status attributable to the recovery of the immune system during ART.”

• Other examples in neurological practice
  - Reversal reactions in leprosy
  - MS relapse following pregnancy
  - Cessation of natalizumab in MS
  - Tuberculoma development in treated-TBM
  - Stroke in *S. pneumoniae* meningitis

IRIS: Classification

Simultaneous = Unmasked
Delayed = Paradoxical

Figure 1. Types of IRIS: IRIS following initiation of HAART may occur in the presence or absence of an opportunistic infection (OI). In some, the OI may first become clinically apparent concurrently with the IRIS and hence termed “simultaneous IRIS.” In others, the OI predates the initiation of HAART but subsequently results in IRIS. This has been termed “delayed IRIS.”

IRIS Associated with CNS Opportunistic Infections

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Frequency</th>
<th>Neuro-IRIS</th>
<th>Extraneural-IRIS</th>
</tr>
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<tbody>
<tr>
<td>JCV</td>
<td>17% (2-50)</td>
<td>Inflammatory PML</td>
<td>None known</td>
</tr>
<tr>
<td>MTB</td>
<td>16% (10-25)</td>
<td>Meningitis; tuberculoma; radiculomyelitis</td>
<td>Lymphadenitis; pulmonary infiltrates; pleural effusions; cutaneous abscess</td>
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<tr>
<td>Cryptococcus neoformans</td>
<td>20% (7-45)</td>
<td>Meningitis; cryptococcoma</td>
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<tr>
<td>MAC</td>
<td>Rare</td>
<td>Tuberculoma</td>
<td>Lymphadenitis; pulmonary infiltrates; pleural effusions; cutaneous abscess</td>
</tr>
<tr>
<td>Toxoplasma</td>
<td>Rare</td>
<td>Encephalitis</td>
<td>Retinitis</td>
</tr>
<tr>
<td>HSV</td>
<td>Rare</td>
<td>Encephalitis; myelitis</td>
<td>Genital ulceration</td>
</tr>
<tr>
<td>VZV</td>
<td>Rare</td>
<td>Vasculitis; myelitis</td>
<td>Dermatomal zoster</td>
</tr>
<tr>
<td>CMV</td>
<td>Rare</td>
<td>Encephalitis</td>
<td>Uveitis; retinitis; colitis</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Rare</td>
<td>Encephalitis; ventriculitis; brain vasculitis</td>
<td>Pure red cell anaemia</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Rare</td>
<td>Encephalitis</td>
<td>Uveitis; ?skin</td>
</tr>
</tbody>
</table>

**IRIS: Clinical Recognition & Management**

**Table 1. Defining features of CNS-IRIS**

| 1. | Worsening of neurological status after initiation of HAART |
| 2. | Deterioration of or new neuroradiological findings suggestive of inflammation |
| 3. | A decrease in plasma HIV viral load of $\geq 1 \log_{10}$ |
| 4. | Symptoms not explained by a newly acquired disease or by usual course of previously acquired illness |
| 5. | Histopathology demonstrating T cell infiltration |

**Differential Diagnosis:**

- Drug toxicity / interaction
- Progression of underlying condition due to:
  - *Resistance of organism*
  - *Poor adherance*
  - *Inadequate drug levels*
- Further pathological process e.g. development of PRES

Conclusions

• Prevent:
  – Vaccinations; preparation & prophylaxis

• History:
  – *How immunosuppressed?*
  – *How long since intervention?*

• May be minimal immune response

• Involve ID/microbiologists/radiologists
  – Laboratory input critical

• Watch for paradoxical reactions with immune reconstitution
References


• Bradshaw (2017) CNS infection associated with immunosuppressive therapy for rheumatic disease. Rheu Clinic N Am 43: 607-619


• Li et al Cerebral phaeohyphomycosis (2009) Lancet Infectious Diseases 9: 376-83


