TBM; Immunopathogenesis

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Reinout van Crevel
What kills TBM patients?

- vascular pathology & hypoxia?
- failure to control *M. tuberculosis* growth?
- ‘collateral damage’ to critical structures?

- what characterises effective and damaging host immune response in TBM patients?
- and what goes wrong at a cellular level?

- and how much of this is genetically determined?
  or can we use genetics to sort cause and effect and identify targets for therapy?
Patients
‘clinical phenotyping’

Laboratory
‘immune phenotyping’

- known / unknown immunodeficiencies or clinical immunopathology
- Immunological phenotyping and/or genetics
- Immune inhibition or stimulation

adjuvant therapy
excessive inflammation (38 female)

- No medical history
- Respiratory infection
- Deterioration over course of 1 month despite multiple courses of antibiotics
- Respiratory failure

Referral:
- CRP 276. 44 leukocytes, 1% lympho’s, 90% PMN
- Ferritin of 16000
- Progressive anemia and trombopenia

- Influenza and aspergillus
Macrophage activation syndrome

- Hematologists: hemophagocytic lymphohistiocytosis
- Primary (kids; mutations affecting cytotoxic T-cells/NK)
- Secondary, triggered by
  - Malignancy (lymphoma)
  - Auto-immune (juvenile RA, Still’s disease, SLE ..) termed MAS
  - Infection (EBV, CMV, influenza...); bacterial
  - Also described in tuberculosis

- Excessive but ineffective immune activation
  - Fever
  - hepatosplenomegaly
  - Lymphadenopathy
  - hemophagocytosis
  - Cytopenia
  - High CRP
  - Low fibrinogen, coagulation disorder
  - High ferritin and triglycerides
  - Elevated transaminases, LDH
  - Elevated sIL2R
macrophage activation syndrome and anakinra

Whole-Exome Sequencing Reveals Mutations in Genes Linked to Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome in Fatal Cases of H1N1 Influenza

Therapeutic Role of Anakinra, an Interleukin-1 Receptor Antagonist, in the Management of Secondary Hemophagocytic Lymphohistiocytosis/Sepsis/Multiple Organ Dysfunction/Macrophage Activating Syndrome in Critically Ill Children*
This session

10:50-11:10 Stroke in TB Meningitis: Path-Physiology, Clinical and Management Issues
   Usha Kant Misra (Sanjay Gandhi Postgraduate Institute of Medical Sciences)

11:10-11:30 Host Genotypes, Inflammatory Response and Outcome of TBM; Vietnam Cohort
   Nguyen Thuy Thuong Thuong (Oxford University Research Unit, Ho Chi Minh City)

11:30-11:50 Host Inflammatory Phenotype and Outcome TBM Indonesia
   Arjan van Laarhoven (Radboud University Medical Center)

Afterwards? Or sometime today / tomorrow

Cerebral tryptophan metabolism is critical in TBM