Meningitis sequelae, their impact, and follow-up care in low income countries – how much do we know?

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MRF Conference 2019
Overview

Global burden of disability and WHO Roadmap

Meningitis sequelae – what do we know

Joseph’s journey through care

Follow-up care in the low income setting

Evaluating neurodisability – the challenges
Childhood neurodisability

One of the most important precursors of:
• psychopathology,
• poor adaptive functioning
• educational disadvantage

Later life
• less likely to be living independently
• be in paid employment or
• have cohabiting relationships

• In era of Sustainable Development Goals there is a renewed emphasis on early child development to maximise the developmental potential for all children

• The Global Strategy supports the need for all children to SURVIVE and THRIVE

• Estimated 53 million children with developmental disability¹

¹ Global Research on Developmental Disabilities Collaborators. *Lancet Glob Health* 2018; 6: e1100–21
Meningitis one of the 4 leading contributors of neurological DALYs

Burden greatest in s-Saharan African region and S Asia

49,844 reported meningitis cases

1670 (3.3%) lab confirmed
Developmental Disabilities among children < 5 years..., 1990-2016. GBD study \textit{Lancet Global Health} 2018

Estimated* 53 million living with disability - 95% living in LMICs
Highest numbers in sub-Saharan Africa (71.3%)
South Asia has highest prevalence of children with developmental disabilities in 2016

*Limited data especially from LMICs & therefore reliance on statistical estimates of trends
The Global Roadmap is based on **five pillars:**

- **Pillar 1:** Prevention and epidemic control
- **Pillar 2:** Diagnosis and treatment
- **Pillar 3:** Disease surveillance
- **Pillar 4:** Support and aftercare for families and survivors
- **Pillar 5:** Advocacy and information

**Pillar 4** - to build and strengthen health systems to provide the necessary care and programmatic support.

- SG11: Strengthen recognition of sequelae both in hospital and by follow up after discharge
- SG12: Increase availability and access to appropriate care for survivors with sequelae
- SG13: Empower survivors and their families to maximize their health and quality of life

- Recognition of **lack of follow-up** post infection and treatment
- Many **sequelae not apparent** on discharge
- Are risks same for each causal agent?
- How is risk decreased with **prompt treatment**?
- Role of **adjunctive therapies** in prevention of sequelae?
Challenges of assessing outcome post bacterial meningitis

- Lack of methodologically sound studies - heterogeneity
- Follow-up time post infection
  - Exclude transient impairments
  - Include later developmental sequelae
- Verification of infection
  - Use of appropriate, clearly described diagnostic methods
- Use of standardised tests in assessment of neurodevelopment

Carter J, Newton CR Brain Res Reviews 2003
Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis

Karen Edmond, Andrew Clark, Viola S Korczak, Colin Sanderson, Ulla K Griffiths, Igor Rudan

Systematic review and meta analysis:
• Jan 1980 to Mar 2008
• Overall risk of disabling sequelae in survivors: 20%
• Proportion with sequelae varied by infecting organism:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Median (%)</th>
<th>IQR (%)</th>
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<tbody>
<tr>
<td>S. pneumonia</td>
<td>24.7</td>
<td>16.2 – 35.3</td>
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<tr>
<td>H. influenza type b</td>
<td>9.5</td>
<td>7.1 – 15.3</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>7.2</td>
<td>4.3 – 11.3</td>
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</table>

Most common types of sequelae:
• Hearing loss – 33.6%
• Seizures 12.6%
• Motor deficit: 11.6%
• Cognitive impairment: 9.1%
• Vision impairments: 6.3%
• Behavioural.............. ?
• 20% impairments involved multiple domains
Carter J
Neurocognitive impairment post CNS infection
- Cognitive, motor and hearing impairments
- Prevalence of epilepsy increasing over time
- Impact of bacterial aetiology

Molyneux E
Edmond K
Disabling sequelae impacted by:
- HIV co-infection
- Younger age

Grimwood K
School age survivors of ABM
- Verbal performance
- IQ
- Reading accuracy
- Visuo-motor integration
- All lower cf controls

Brain Res Rev 2003
ADC 2003; Lancet ID 2010
Paediatrics 1995
Hearing loss post ABM – a Silent Crisis?

- High prevalence of SNHL post ABM (but not TBM)
  - ~6% of all acquired SNHL in children
- Studies of incidence and cause of HL post ABM are limited
  - Quality of audiometry variable
  - Severity and timing of HL inconsistently reported
- Early referral needed for optimum outcome

Hearing Outcomes in Children with Meningitis at RCWMCH
Kuschke et al SAMJ

- Retrospective review Jan 15-Jun 16
- 68 cases (12 confirmed)
  - Only 16 (23.5%) referred
  - Overall prevalence of HL: 42.8%
  - 28.5% severe to profound
- Late referrals/lack of awareness amongst health professionals

Lack of sufficient or quality hearing input during early childhood
- Poor speech and language
- Poor academic development
Pathophysiology and developmental outcome of TB meningitis

- **Arterial ischaemic stroke** likely main cause of irreversible neurological damage
- **Infarction** commonly occurs in the basal ganglia and associated with:
  - language delay, spatial neglect, executive dysfunction, autism and attention deficit hyperactivity disorder (ADHD). *Riva 2019*
- The **most common impairments** at follow-up are in:
  - cognition, learning, emotion and behaviour
- Poor neurodevelopmental outcome is associated with:
  - younger age
  - delayed presentation and treatment initiation
  - multiple, bilateral and large infarctions
  - clinical severity
  - hydrocephalus. *Schoeman 2002; van Well 2009; Humphries 1990*
- Persistent visual and hearing deficits uncommon *Schoeman 2002*
Impact of bacterial meningitis on families and communities:

- Survivors – at risk of long-term disabling sequelae
  - Hidden from view in many societies
  - Subjected to stigma and neglect (Nakayama & Tann, 2013)
  - Undercounted in national and international statistics
- Few data sources on risk of disability
  - severity and distribution of sequelae
- Financial burden on families – often not calculated or underestimated

Image courtesy of Anna Vines, World Hope
Joseph’s story

- Previously thriving and active toddler
- ABM at 2 years
- Treated IV antibiotics for 5 days
- Discharged to home - no follow-up
- Abandoned by mother - cared for by elderly grandmother
- Presented at 10 years of age with:
  - Severe dysphagia and failing to thrive
  - Four limb Cerebral palsy
  - Epilepsy – biting through bottom lip
  - Non-verbal and ? hearing
Joseph’s story

- Assessed by visiting Speech and language therapist
  - Positioning/feed thickeners
- Admitted to local hospital for NGT feeding
  - Gastrostomy inserted using catheter tubing
- Followed up Cheshire Homes
- ‘Rehabilitation’ and donated wheelchair
- Epilepsy - Phenobarbitone
- Travel to clinic costly – loss to follow-up
Follow-up care in low income settings (LICs)

- Limited resources and facilities for children and adults with disabilities
- Fragmented
- Provision often by NGOs, charitable and civil society organisations
- Expensive!
  - Average life time cost for meningitis sequelae in Dakar, Senegal:
  - Est. $35,000 – 98% for childcare and productivity; *Edmonds PIDJ 2012*
## Therapy Services

### Public Sector Services
- Very limited resources
- Enormous workload – stroke and trauma rehab
- Often serving very large geographical areas
- No/limited outreach services
- Costly private provision

<table>
<thead>
<tr>
<th></th>
<th>Kalawati Saran Children’s Hospital</th>
<th>PGIMER</th>
<th>Edward Frances Small Teaching Hospital</th>
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<tbody>
<tr>
<td>Population served</td>
<td>~2 million</td>
<td>60-80 million</td>
<td>1.6 million</td>
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<tr>
<td>Annual admissions</td>
<td>25 000</td>
<td>30 000</td>
<td>?</td>
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<tr>
<td>Neurology neurorehab Drs</td>
<td>4</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Physiotherapists</td>
<td>4</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Occupational therapists</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Speech and language</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Wheelchair services</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>
What hearing/ENT services are there in sub-Saharan Africa?

**Gambia:**
- Population: ~1.6 million
- NO qualified audiologists
- No native ENT surgeons
- 2 schools for the deaf

**Sierra Leone:**
- Population: ~5.25 million
- NO qualified audiologists
- No native ENT surgeons
- 2 schools for the deaf

**Zambia:**
- Population: ~17 million
- 1 audiologist
- 2 ENT surgeons
- 6 schools for the deaf

**Cameroon:**
- Population: ~16.38 million
- NO qualified audiologists
- 37 ENT surgeons
- Several schools for the deaf – none government funded

**Malawi:**
- Population: ~18 million
- 3 audiologists
- 2 ENT surgeons
- 6 schools for the deaf

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**Sound Seekers**
- Train local health professionals to deliver ear and hearing health services
- x3 Malawi graduate students in MSc audiology programme in UK
- Train school teachers in hearing loss awareness
- Support inclusion of children with HL in schools
- Rights and advocacy

Hearing aids improve communication in up to 90%
In LMICs, <1:40 who need a hearing aid have one
Physiotherapy Services in Freetown Sierra Leone

- Rehabilitation Centre
  - World Hope International
- Provision of equipment:
  - Splints, chairs, standing frames
  - Few children brought to centre
  - Local staff afraid to work with disabled children

Challenges identified
- Limited knowledge of disability
- Stigmatisation
  - Local belief system that child possessed by demons/cursed
  - Seizures ‘witched’
  - Encouraged by local Chiefs, religious leaders
- Parents refusing to complete therapy – fear of demons
- The disabled child blamed by community for any mishap
Overcoming challenges to providing therapy in Sierra Leone

- Outreach care – home-based therapy across Freetown
- School visits – supply of seating/tables
- Basic feeding
- Empowerment and peer support to carers
  - Reducing self-stigmatisation
  - Improving confidence
- Healthcare worker support and training
- Support from high profile citizens

- Therapy training programme
- 2 year certificate training for rehabilitation assistant
- Basic competencies assessed to become a Rehabilitation Therapist
- Now a large team
  - Therapists/assistants and trainees
  - Support workers
  - Pastoral and educational support workers
- Electronic records!
- Ongoing M&E
Evaluating neurodisability

To understand and characterise impairment requires:
• Appropriately developed neurodevelopmental assessment tools
  • early identification and treatment of disability
  • improve opportunities for developmental change and rehabilitation

Challenges:
• Lack of robust, standardised assessment tools
• Developed for and normed across geographical and cultural settings
• Most NDATs developed in High Income Settings
• Tools often ‘adapted’ for LICs
  • May not evaluate same construct across
Development affected by – Illness, malnutrition......Violence, abuse, neglect

<table>
<thead>
<tr>
<th>0-5 YEARS</th>
<th>6 YEARS AND BEYOND</th>
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<tbody>
<tr>
<td>EARLY DEVELOPMENTAL SKILLS</td>
<td>DOMAIN SPECIFIC</td>
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<tr>
<td>Language, Motor</td>
<td>Emerging executive function, attention</td>
</tr>
<tr>
<td>Visual-receptive</td>
<td>Emotional and behavioural function</td>
</tr>
</tbody>
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Developmental Skills

0-5 YEARS
0  1  2  3  4  5  6  7  8  9  10  15  20

AGE (years)

0-5 YEARS
- Language
- Motor

6 YEARS AND BEYOND
- Executive function
- Emotional function

ASQ
- Wechsler Intelligence Scale for Children

Bayley Scale

MSEL/Griffiths

Kauffman Assessment Battery

Vineland

Kilifi Developmental Checklist

Malawi Developmental Assessment Tool (MDAT)

WHO Indicators of Infant and Young Child Development
Opportunity to complete prospective longitudinal studies
Linked to diagnostic platforms and evaluation of new treatment interventions

Lack of standardised methodology to assess global neurodevelopment across geographically & culturally diverse population groups

Lack of consensus on optimal tools for assessing outcome post CNS infection in both adults and children

Adapted from Fernandes et al PlosOne 2014
THE SURE TB MENINGITIS TRIAL

Multi-site, partially blinded RCT of WHO standard of care vs Short intensive 4 drug regimen Factorial “2 for 1” design

Primary Outcome – ATT arm
All cause mortality at 48 weeks

Primary outcome – Aspirin arm
Motor outcome at 48 weeks

Substudy:
Longitudinal neurodevelopmental outcome

Children aged <15 years with TB meningitis (n = 400)

RANDOMISATION 1

Interventional arm
6H*R*ZL (n = 200)
6 H(20)R(30)Z(40)L(20)

Control arm (WHO regimen)
2HRZE 10HR (n = 200)

RANDOMISATION 2

Anti - TB

Aspirin
20mg/kg (n = 200)

Placebo
(n = 200)

Anti - Inflammatory

Steroids - SOC

6H^HD_R^HDZL = INH 20mg/kg, *High Dose RMP 30-35mg/kg*, PZA 40mg/kg and LFX 20mg/kg; (+PK)
Assessing Neurodevelopmental outcome requires:

• Standardised, locally normed, functional and neurocognitive assessments

• That vary by age targeting:
  <5 years - early developmental skills

• ≥5 years – cognitive, functional, behaviour and attention

• No requirement for costly or extensive staff training

• Uniform methods for adapting existing NDATs
  • Translation/back translation
  • Adjustment of stimuli for cultural variables
  • Healthy control group

Summary

• For survivors of meningitis the long-term outcome maybe uncertain
• Significant long-term sequelae:
  • Sensory, neurocognitive, functional and behavioural/psychiatric impairment
• Need for high quality, prospective, longitudinal outcome studies demonstrating the disease’s impact:
  • further support advocacy for improved meningitis prevention programmes
  • required to assess the resource burden
  • effectiveness of treatment interventions
Acknowledgements

• **Anna Vines – World Hope Sierra Leone**
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• **Suvasini Sharma – Kalawati Saran Children’s Hospital, Delhi**
• [https://www.youtube.com/watch?v=y6L_91xtbjw](https://www.youtube.com/watch?v=y6L_91xtbjw)
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