

Long-Term Sequelae of Childhood TB meningitis

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Stellenbosch

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IYUNIVESITHI
UNIVERSITEIT

forward together
sonke siya phambili
saam vorentoe



**“Have no fear of perfection,
you’ll never reach it”**

- Salvador Dali

Contents

- Introduction.
- Outcome of childhood TBM.
- Predictors linked to poor outcome.
- Time line assessment of CTBM.
- Review of studies addressed NS among survivors.
- What happens after childhood TBM in adolescents and adult life?(MPhil study project proposal).
- Conclusion.



Introduction

- TB affects 10 million people globally each year.
- TBM is the most common and debilitating form of CNS TB.
- True incidence of TBM is unknown (2-10% all TB cases).
- CNS TB manifests with a variety of clinical presentations.
- Depending on the *site of lesion* and *extent of infection* CNS TB can be classified into different entities.

M. A. Schaller et al clinical neuroradiology ,2019

World health organization TB report ,2021

Introduction (TBM-Case Definition)

- A definite case of TBM based on:
 - ✓ histopathological changes of TB in brain or spinal cord on autopsy / or
 - ✓ fulfil 2/2 of the following :clinical criteria &laboratory evidence of TB.
- Probable TBM: Clinical entry criteria plus a total diagnostic score of 10 to 12 points.
- Possible TBM: Clinical entry criteria plus a total diagnostic score of 6–11points.

Introduction (TBM-Case Definition)

Clinical criteria	(Maximum category score=6)
Symptom duration of more than 5 days	4
Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks	2
History of recent (within past year) close contact with an individual with pulmonary tuberculosis or a positive TST or IGRA (only in children <10 years of age)	2
Focal neurological deficit (excluding cranial nerve palsies)	1
Cranial nerve palsy	1
Altered consciousness	1
CSF criteria	(Maximum category score=4)
Clear appearance	1
Cells: 10–500 per μ l	1
Lymphocytic predominance (>50%)	1
Protein concentration greater than 1 g/L	1
CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2.2mmol/L	1
Cerebral imaging criteria	(Maximum category score=6)
Hydrocephalus	1
Basal meningeal enhancement	2
Tuberculoma	2
Infarct	1
Pre-contrast basal hyperdensity	2
Evidence of tuberculosis elsewhere	(Maximum category score=4)
Chest radiograph suggestive of active tuberculosis: signs of tuberculosis=2; miliary tuberculosis=4	2/4
CT/ MRI/ ultrasound evidence for tuberculosis outside the CNS	2
AFB identified or <i>Mycobacterium tuberculosis</i> cultured from another source—ie, sputum, lymph node, gastric washing, urine, blood culture	4
Positive commercial <i>M tuberculosis</i> NAAT from extra-neural specimen	4
Exclusion of alternative diagnoses	
An alternative diagnosis must be confirmed microbiologically (by stain, culture, or NAAT when appropriate), serologically (eg, syphilis), or histopathologically (eg, lymphoma). The list of alternative diagnoses that should be considered, dependent upon age, immune status, and geographical region, include: pyogenic bacterial meningitis, cryptococcal meningitis, syphilitic meningitis, viral meningo-encephalitis, cerebral malaria, parasitic or eosinophilic meningitis (<i>Angiostrongylus cantonesis</i> ,	

Introduction

- Early CT scan can be normal .
- presence of high density within the basal cisterns on non-contrast CT scans is a very specific sign for childhood TBM .
- The most common brain CT scan findings were hydrocephalus (86.1%)and basal meningeal enhancement(75%).

Farinha NJ, Journal of infection,2000.

AndronikouS, paediatric radiology,2004

Padayatchi N, The Pediatric infectious disease journal. 2006

Van Well ,Pediatrics ,2009.

Treatment update and expertise recommendation

TBM in children

- HIV negative :anti TB meds intensive short 6 months
- HIV positive :anti TB meds for 9 months
- Rif at higher dose is safe and effective.
- With Prednisone 2mg/kg/day for 4 weeks then tapering over 2 weeks.

Hyponatremia (cerebral salt wasting /SIADH)

- Avoid fluid restriction
- slow correction of Na with hypertonic saline at 1 mmol/L/h

Hydrocephalus(multifactorial)

- Medical therapy, furosemide 1 mg/kg/day and acetazolamide 50–100 mg/kg/day, given for 1 month, has been shown to normalize raised ICP within 7 days of treatment

Noncommunicating hydrocephalus treated by neurosurgical CSF diversion

Treatment update and expertise recommendation

- Vasculitis
- Cerebral venous sinus thrombosis
- Arterial ischemic infarction(BG, Thalamus and brain stem).

The Role of Aspirin in Childhood Tuberculous Meningitis

Johan F. Schoeman, MD¹,
Anita Janse van Rensburg, Dip Nurs, KIDCRU¹,
Jacoba A. Laubscher, B Com², and Priscilla Springer, FCP¹

- No current evidence that Aspirin improves outcome.
- There is still ongoing Paediatric trials.

Update on the Treatment of Pediatric Tuberculous Meningitis

Regan S. Solomons¹, PhD,* Ronald van Toorn², PhD,* Fiona V. Cresswell³, PhD,†‡§
and James A. Seddon⁴, PhD*¶

THE LANCET Neurology

Volume 21, Issue 5, May 2022, Pages 450-464



Review

Tuberculous meningitis: progress and remaining questions

Huynh J, The Lancet Neurology. 2022
Solomons RSs The Pediatric Infectious Disease Journal, 2022

Schoeman JF, Journal of child neurology. 2011.

Treatment update and expertise recommendation

- Tuberculoma in the critical area
- TB abscess
- Optochiasmatic arachnoiditis (IRIS)

- Seizure meningeal irritation, cerebral oedema, hydrocephalus ,infarct or tuberculoma.

- Adverse reaction to antiTB meds
- Ethionamide related
- Hepatotoxicity(DILI) related to Rif/INH and Pyz

- Thalidomide as adjunctive might be helpful.

- No clinical trial to identify the best management (uncertain)

- Ethionamide can be given noct .
- Monitor TFT If hypo occurred treat with thyroxine.
- Resolved after stop Ethionamide
- No completed clinical trials

Huynh J,The Lancet Neurology. 2022

Solomons RSs The Pediatric Infectious Disease Journal,2022

Outcome of Childhood TBM

Death

- Mortality rate 5.5% to 23.9%.
- Intensive 6 short regimen has mortality rate 5.5% vs 12 month regimen has 23.9%.

survival with sequelae

- Motor, sensory , hypothalamic ,cognitive impairment occur during illness and persist .
- among survivors 53.9%.
- In UK permanent neuro S documented in 47%
- SA study in 71% and European NS of 19.2% .In WHO 12 months of treatment 36.3% while 6 months is 66%

survival without sequelae

- 15.8% to 36.7%

Farinha NJ, Journal of infection,2000. Van Well ,Pediatrics ,2009

Chiang SS, The Lancet Infectious Diseases. 2014 Thee S Clinical Infectious Diseases. 2022

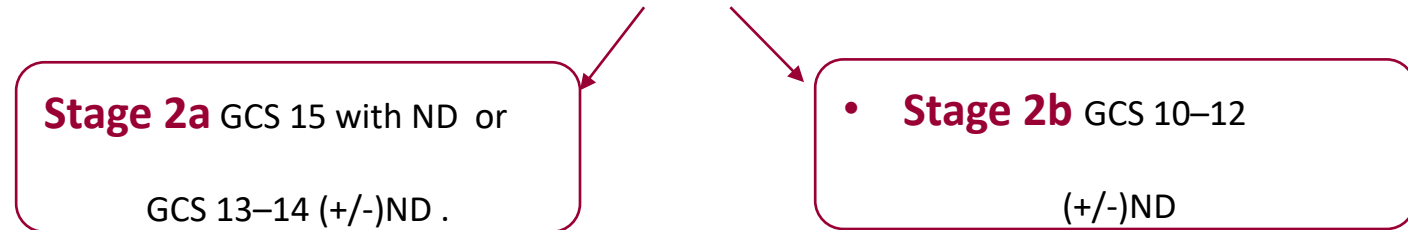
Sulis G.In Open Forum Infectious Diseases 2022

Prediction of childhood TBM outcome

○ Modified MRC staging 1974

Stage 1	Stage 2	Stage 3
GCS of 15 with no ND	GCS of 15 with ND or GCS of 11–14(+/-) focal ND	GCS of ≤ 10 . with ND.

○ Refined MRC staging



Streptomycin Treatment of TBM. 1948

Prediction of childhood TBM outcome

○ TBAN score 2005

coma	semicoma	lethargy	Un.Seizure	C.seizure	CNP	F.motor	Inc tone
3	2	1	2	1	1	1	1

○ TCH 2011

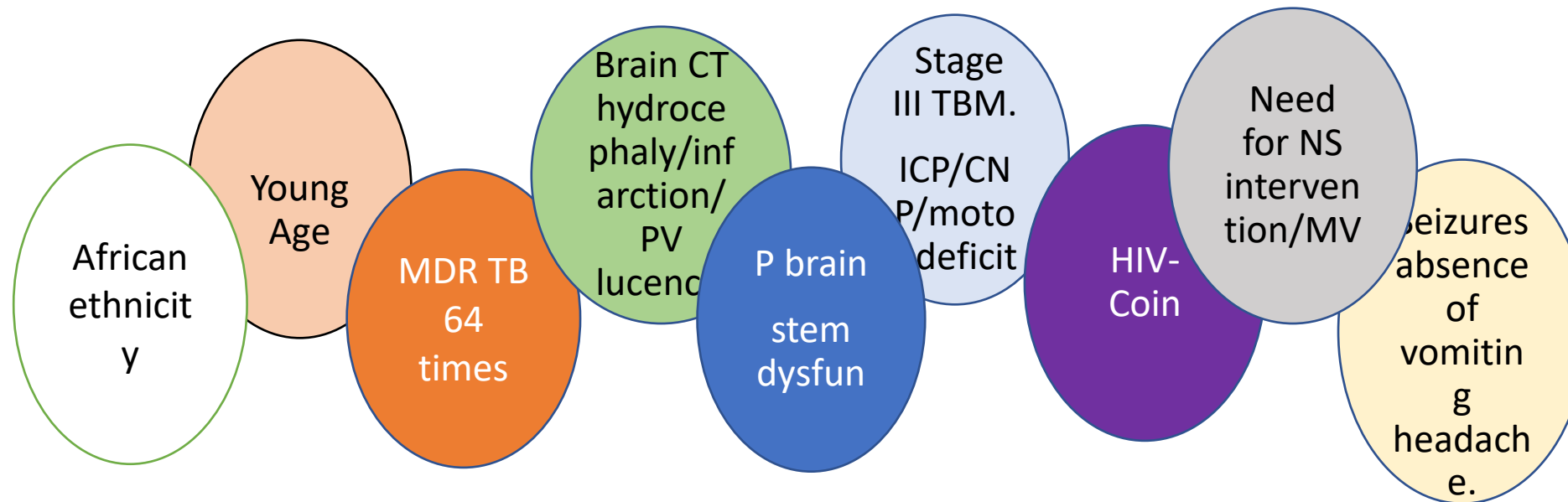
○ The refined MRC scale 1 week after diagnosis showed the best association with neurological outcome after 6 months of treatment.

Saitoh A .The Pediatric infectious disease journal ,2005

Van Toorn R The International journal of tuberculosis and lung disease, 2012

Stage 1	Stage 1	Stage 2a	Stage 2b	Stage 3
Fix and follow	Yes	Yes	No	No
Localize pain	localise on both sides	localises pain on one side	localise on one or both sides	Unable to localise pain

Predictors of poor outcome



Schoeman J Developmental Medicine & Child Neurology, 2002

Marais S, The Lancet infectious diseases. 2010

van Toorn R. Seminars in pediatric neurology 2014

• *Thee S Clinical Infectious Diseases. 2022*

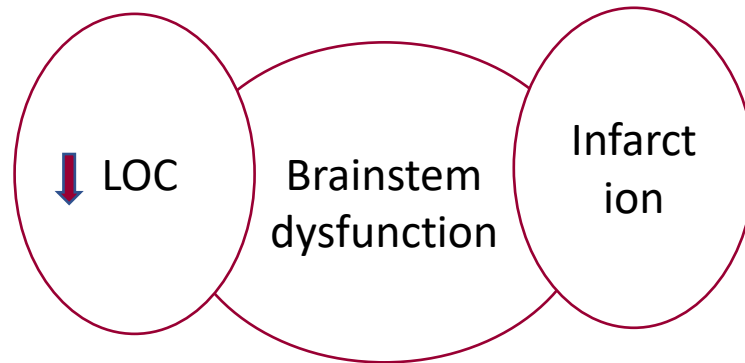
Van Well GT, Pediatrics, 2009

Van Toorn R, The International journal of tuberculosis and lung disease, 2012

Chiang SS, The Lancet Infectious Diseases. 2014

Sulis G. In Open Forum Infectious Diseases 2022

Predictors linked to severe DD among survivors



- Bilateral infarctions associated with worse DQ.
- Basal ganglia damage associated with language delay, spatial neglect, executive dysfunction, autism, and ADHD.

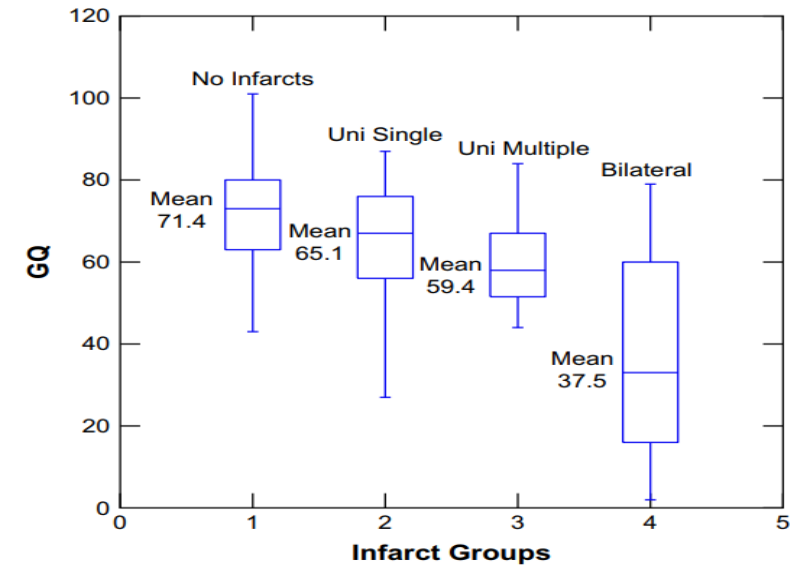


Fig. 1 – General Quotient (GQ) distribution for the four different infarct groups (including means).

Springer P, European journal of paediatric neurology. 2009

Solomons RS Child's Nervous System. 2021

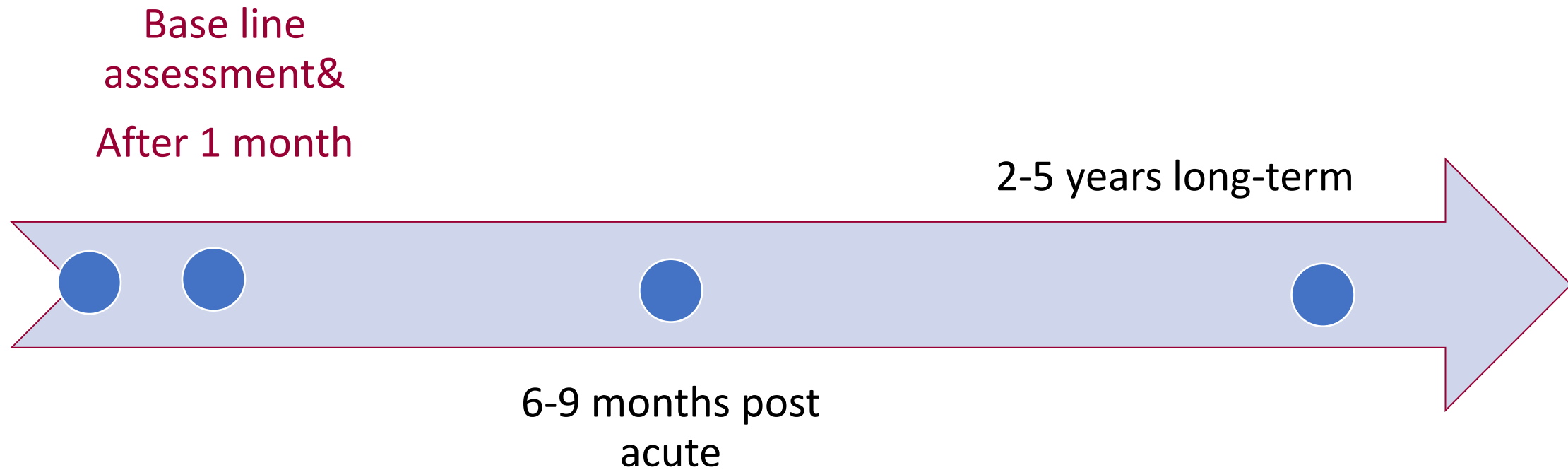
C-L Saal, Risk Factors for Neurodevelopmental Delay in Children with Tuberculous Meningitis (unpublished)

Once Anti TB treatment completed

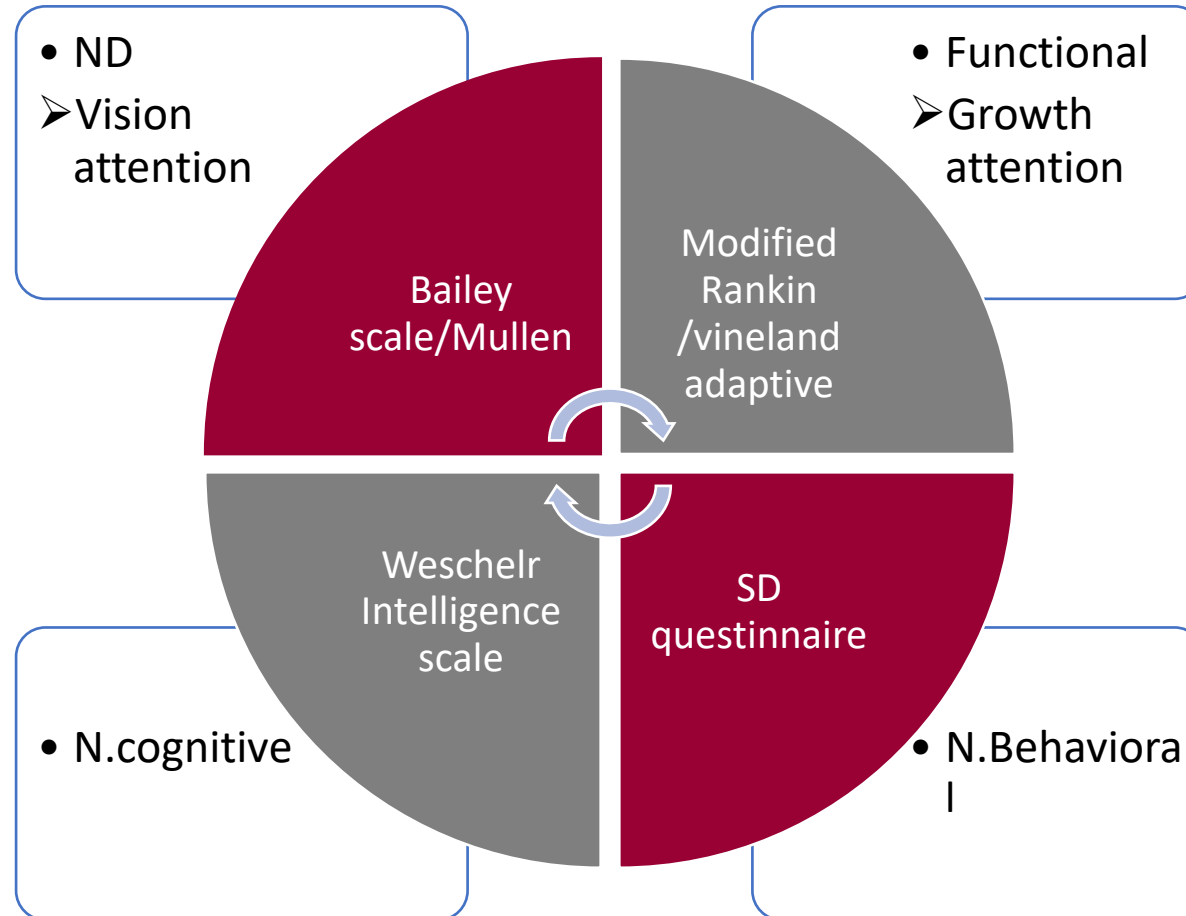
What Is Next ???



Timeline assessment of Childhood TBM



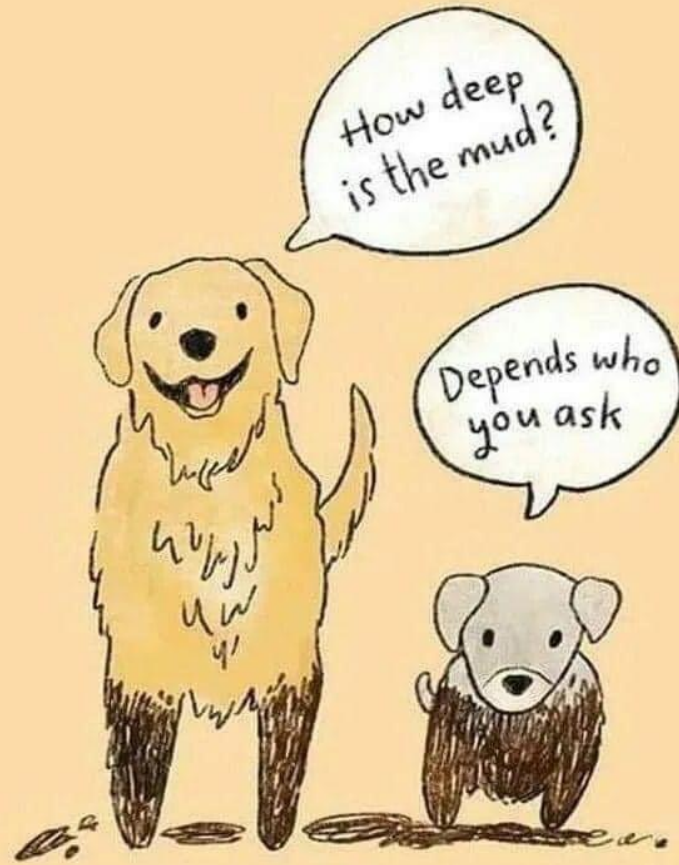
Assessment of Neurological Outcome Among Survivors



Multidisciplinary Team

- ✓ Neurologist seizure control.
- ✓ Neurosurgeon VP shunt monitoring
- ✓ Developmental /Psychologist (aware of possible outcome & validated screening tool available).
- ✓ Social worker
- ✓ Physio/ OT & speech
- ✓ Dietician
- ✓ Ophthalmology & Audiology
- ✓ Paediatrician & **PHC**





WE ALL GO THROUGH
THINGS DIFFERENTLY

Review of Studies addressed NS of CTBM

Ct ,year	Number	motor	cognitive	sensory	behaviour	epilepsy	social	P.school	Somatic /job
1.UK,61	100	12%	6%	13%	15%	8%	-	31% D	-/shop
2.UK,64	65	33%	9.2%	4%	44%	70%	-	13.8%	12.3%/-
3.USA,75	21	40% NS	38%	57%	57%	9.5%	-	23.8% no	-/57%
4.India,89	100	53% NS	-	5%	19%	14%	-	-	-/-
5.UK,200	38	27%	13%	27%	17%	-	-	-	-/-
6.SA,002	76	25%	80%	1.3% B	40% Em	-	-	43%	13%/-
7.SA,002	21	-	-	-	All ADHD s/s	-	-	-	-/-
8.SA,009	74	-	-	-	>10% risk	-	-	-	-/-
9.SA,009	554	54%	M 57.7% S 19.5%	8.9%	-	-	-	-	-/-
10.Indone sia ,16	29	57%	57%	40%v39% H	-	-	-	-	-/-

Health related quality of life of Childhood TBM

○ 48 survivors were assessed in 6 domains :

sense, mobility, emotion, cognition, self care and pain.

✓ 10 out 48 had normal QoL

✓ 13 out 48 had one impairment

✓ 25 out of 48 had multiple impairment

Long-term follow up of childhood tuberculous meningitis

J Schoeman MD ✉, J Wait PhD, M Burger Hons BSc, F van Zyl MSc, G Fertig MB ChB, A Janse van Rensburg, P Springer FCP (SA), P Donald MD

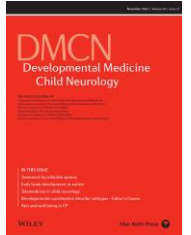


Table I: Main concerns of parents during follow-up visit

<i>Concern</i>	<i>Number</i>
None	34
Behaviour	17
Headache	10
Poor scholastic progress	6
Other	13
Deafness	1
Blindness	1
Weakness (clumsiness)	5
Enuresis	1
Drooling	1
Seizures	1
Non-specific	3

Review of Studies addressed NS of CTBM

Ct ,year	Number	motor	cognitive	sensory	behaviour	epilepsy	social	P.school	Somatic /job
1.UK,61	100	12%	6%	13%	15%	8%	-	31% D	-/shop
2.UK,64	65	33%	9.2%	4%	44%	70%	-	13.8%	12.3%/-
3.USA,75	21	40% NS	38%	57%	57%	9.5%	-	23.8% no	-/57%
4.India,89	100	53% NS	-	5%	19%	14%	-	-	-/-
5.UK,200	38	27%	13%	27%	17%	-	-	-	-/-
6.SA,002	76	25%	80%	1.3% B	40% Em	-	-	43%	13%/-
7.SA,002	21	-	-	-	All ADHD s/s	-	-	-	-/-
8.SA,009	74	-	-	-	>10% risk	-	-	-	-/-
9.SA,009	554	54%	M 57.7% S 19.5%	8.9%	-	-	-	-	-/-
10.Indone sia ,16	29	57%	57%	40%v39% H	-	-	-	-	-/-



Volume 56, Issue 3

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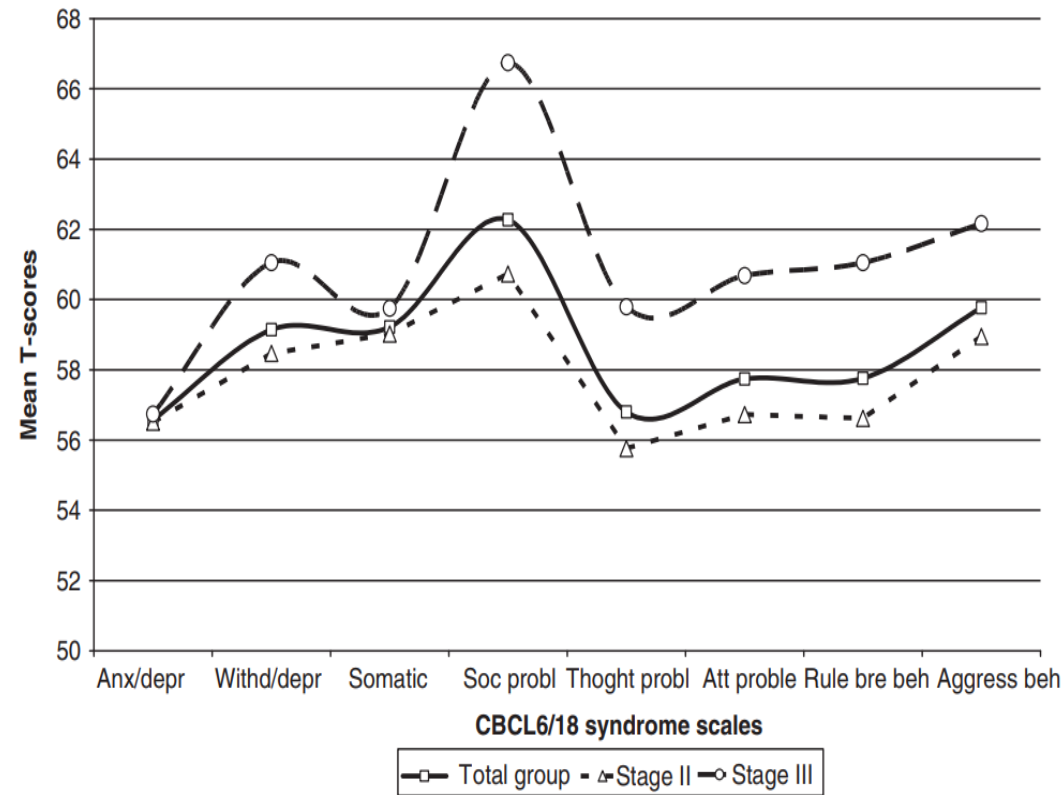
Behaviour Profiles After Tuberculous Meningitis

J. W. Wait, J. F. Schoeman

Journal of Tropical Pediatrics, Volume 56, Issue 3, June 2010, Pages 166–171,

<https://doi.org/10.1093/tropej/fmp080>

Published: 26 August 2009



What happens after Childhood TBM in adolescents and adult life



Describe QOL in adolescents and adult survived CTBM

- Health outcome:

physical health: pain, easy to access health care, and satisfaction with service provided.

Mental wellbeing: self esteem, depression and anxiety

- Level of dependency (functionality)

Independent /still living with parents /totally dependent with multiple health concerns.

- Academic outcome:

Graduate/drop out of school/still schooling

- Behavioural outcome (legal)

Poor self-control, Substance dependence, criminal conviction, and incarceration.

- Financial outcome:

Government assistance, Job in government, self-employed, unemployed.

- Social outcome (family notion)

Good relations with family members, friendship, in long term relationship , married , single and single-parent households.

Benefit of proposed study

- Describe Social , psychosocial and socioeconomic characteristics among survivors that might influence public health policy.
- Help to design targeted interventional programs (rehabilitation) to address their limitations.
- As a result :
 - ✓ Minimize the cost and crime rate.
 - ✓ Increase adult productivity.
 - ✓ Improve QOL .

Conclusion

- ❑ TBM has a huge influence on the affected children's developmental trajectory and behaviour shaping their future adult life.
- ❑ Despite advances in treatment and diagnostic approaches, the TBM burden continues to exhaust the medical ,educational and socioeconomic systems in our community.
- ❑ Lack of socioeconomic and qualitative researches that address the patients and families perspective on disease (quality of life).
- ❑ Standardize surveillance and follow up programs post childhood TBM is essential to improve long term outcome .

Reference of Review of studies addressed NS

1. Lorber J. Long-term follow-up of 100 children who recovered from tuberculous meningitis. *Pediatrics*. 1961 Nov;28(5):778-91.
2. Gilder SS. What Happens After Tuberculous Meningitis?. *Canadian Medical Association Journal*. 1964 Sep 9;91(13):720.
3. Sumaya CV, Simek M, Smith MH, Seidemann MF, Ferriss GS, Rubin W. Tuberculous meningitis in children during the isoniazid era. *The Journal of Pediatrics*. 1975 Jul 1;87(1):43-9.
4. Ramachandran P, Duraipandian M, Reetha AM, Mahalakshmi SM, Prabhakar R. Long-term status of children treated for tuberculous meningitis in south India. *Tubercle*. 1989 Dec 1;70(4):235-9.
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6. Schoeman J, Hons MB, Van Zyl F, Fertig G, van Rensburg AJ, Springer P, Donald P. Long-term follow up of childhood tuberculous meningitis. *Developmental Medicine & Child Neurology*. 2002 Aug;44(8):522-6.
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8. Wait JW, Schoeman JF. Behaviour profiles after tuberculous meningitis. *Journal of tropical pediatrics*. 2010 Jun 1;56(3):166-71.
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10. Nataprawira HM, Ruslianti V, Solek P, Hawani D, Milanti M, Anggraeni R, Memed FS, Kartika A. Outcome of tuberculous meningitis in children: the first comprehensive retrospective cohort study in Indonesia. *The International Journal of Tuberculosis and Lung Disease*. 2016 Jul 1;20(7):909-14.

Suggested Reading

1. Huynh J, Donovan J, Phu NH, Nghia HD, Thuong NT, Thwaites GE. Tuberculous meningitis: progress and remaining questions. *The Lancet Neurology*. 2022 May 1;21(5):450-64.
2. Solomons RS, van Toorn R, Cresswell FV, Seddon JA. Update on the Treatment of Pediatric Tuberculous Meningitis. *The Pediatric Infectious Disease Journal*. 2022 Apr 11:10-97.
3. Davis AG, Nightingale S, Springer PE, Solomons R, Arenivas A, Wilkinson RJ, Anderson ST, Chow FC, Tuberculous Meningitis International Research Consortium. Neurocognitive and functional impairment in adult and paediatric tuberculous meningitis. *Wellcome Open Research*. 2019;4.
4. Sulis G, Tavaziva G, Gore G, Benedetti A, Solomons R, van Toorn R, Thee S, Day J, Verkuijl S, Brands A, Viney K. Comparative effectiveness of regimens for drug-susceptible tuberculous meningitis in children and adolescents: a systematic review and aggregate-level data meta-analysis. *InOpen Forum Infectious Diseases* 2022 Jun (Vol. 9, No. 6, p. ofac108). US: Oxford University Press.

Thank you

A hand is pointing towards two wooden blocks stacked on a dark surface. The top block is slightly offset to the right and contains the word "ANY". The bottom block is wider and contains the word "QUESTIONS?".

ANY
QUESTIONS?