Monsieur M., 24 ans

Dr Adeline MAMBIE
CH DOUAI
JRPI 2024

ATCD

- Inconnus
- Traitement?
- Allergies?
- Mode de vie?
- Patient réfugié Afghan, centre accueil croix rouge entre 08/23 et 01/24

HDM, EXAMEN CLINIQUE

- Le 11/02/24 : troubles de conscience contexte fébrile.

  - HD stable, 40°C, sat 100% AA
  - Glasgow<11, épisode agitation, aphasie
  - Pas de syndrome méningé
  - Auscultation RAS
  - Cutanéo-muqueux RAS

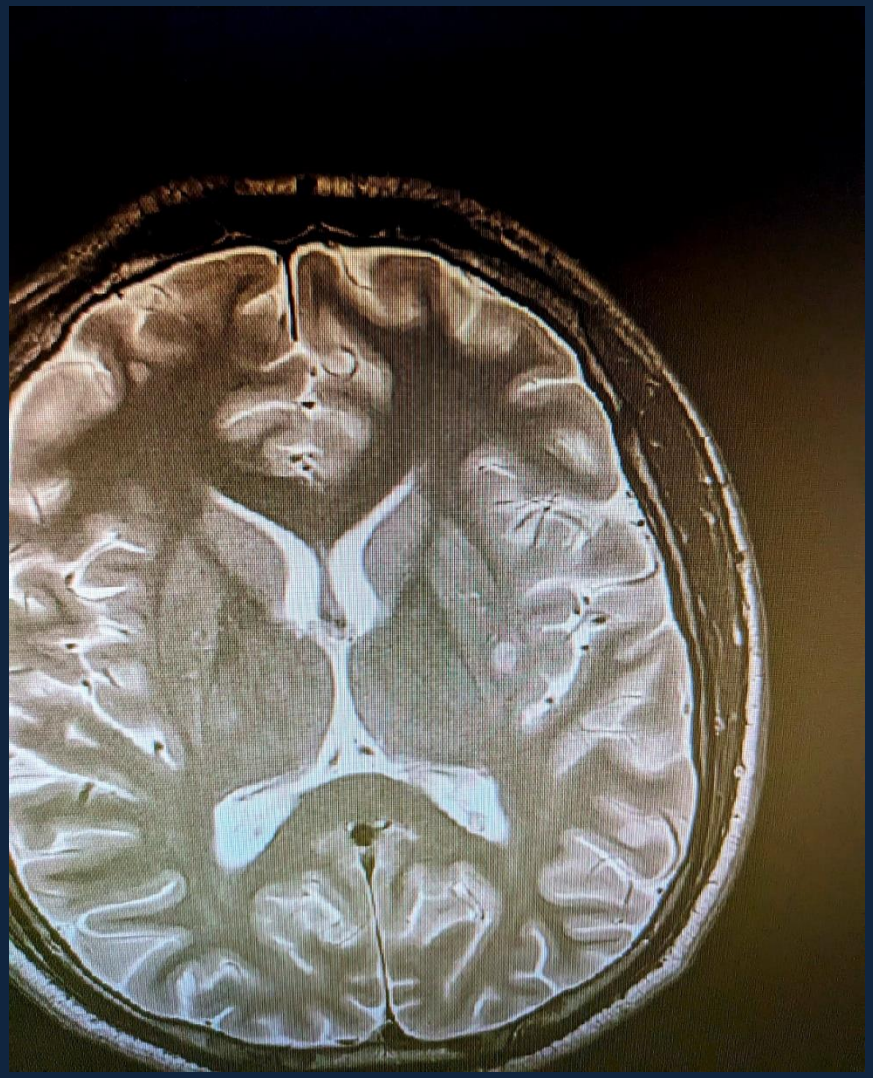
EXAMENS COMPLEMENTAIRES

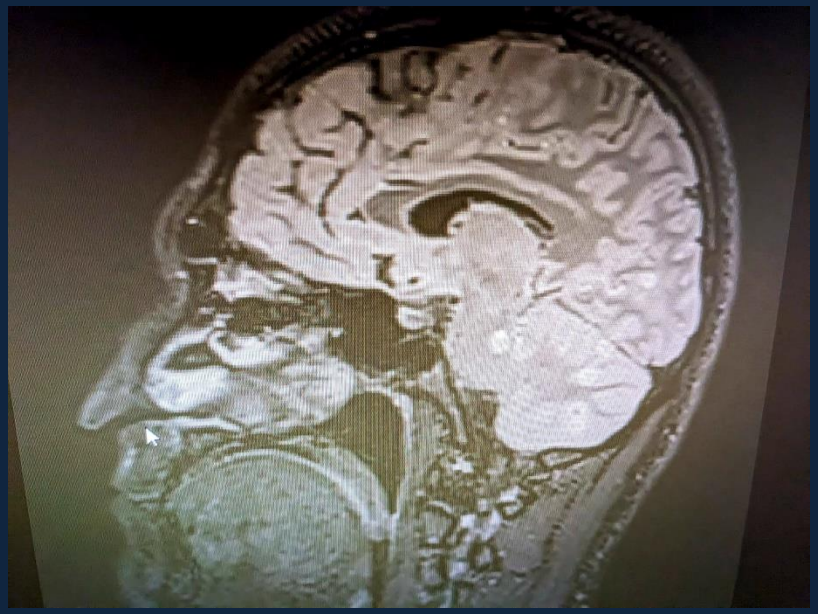
- TDM cérébral RAS
- Bilan toxicologique négatif
- CRP 14mg/L, GB 8G/L (PNN), Na+ 130 mmol/L

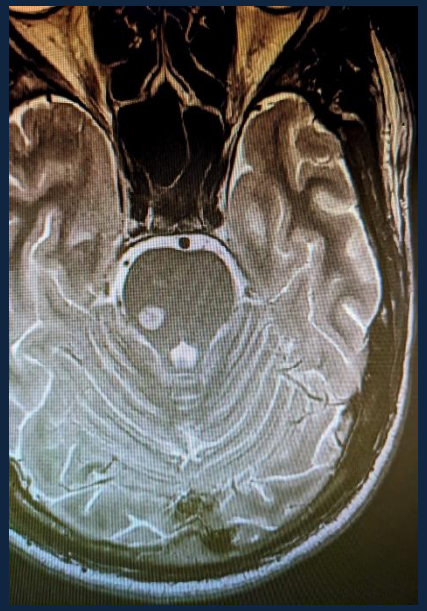
- PL:
  - GB = 220/mm3 (77% PNN, lympho 17%), GR 2700/mm3
  - glycorachie 22mg/L (rapport LCR/sang < à 0,5),
  - lactates = 63 mg/L (9-26),
  - protéinorachie 1500 mg/L (150-450)
  - ED négatif

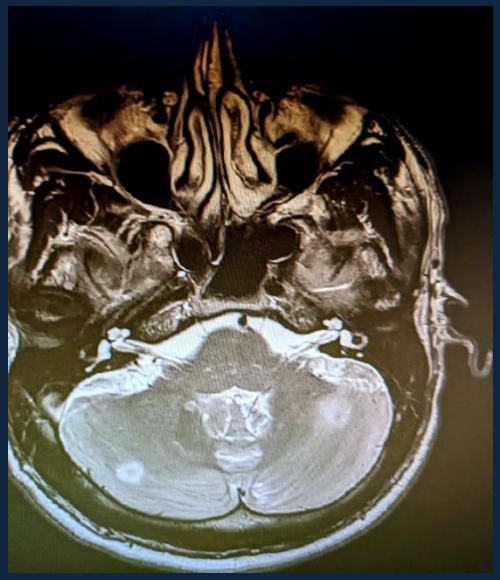
EXAMENS COMPLEMENTAIRES

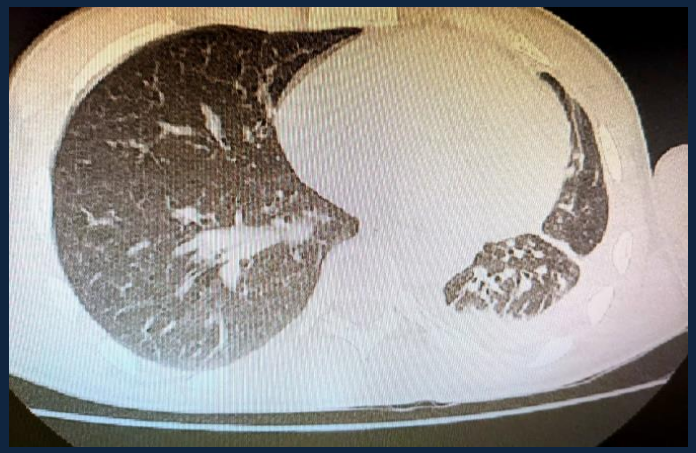
- Radio thorax : épanchement pleural G faible
- TDM TAP : idem + microlacunes hépatiques, adénoP para-aortique G niveau L2L3
- Séro VIH négative, syphilis négative, hépatites B/C négatives
- Hémocultures stériles
- PCR multiplex LCR et culture négatives
- IRM c : …

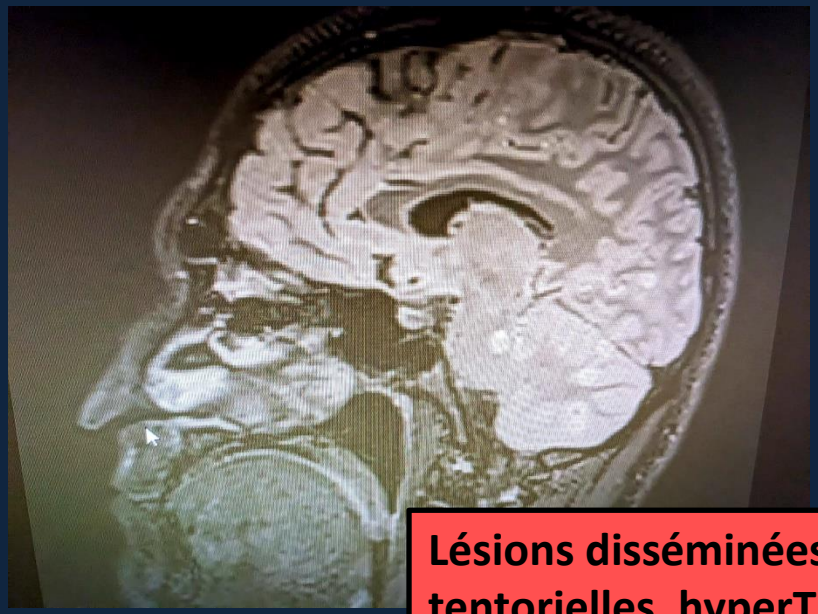


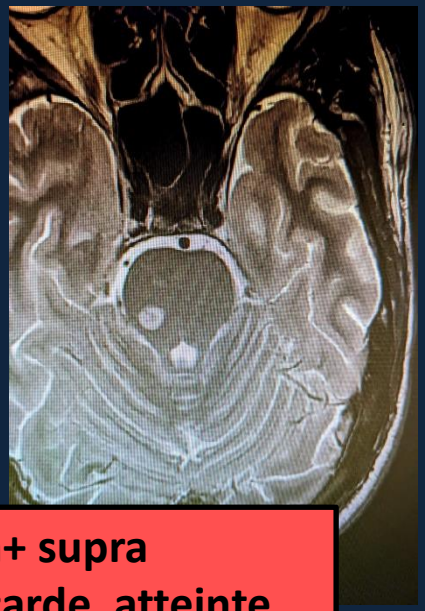




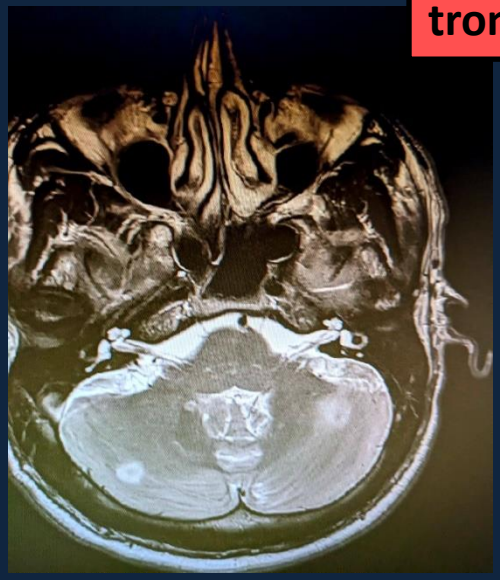


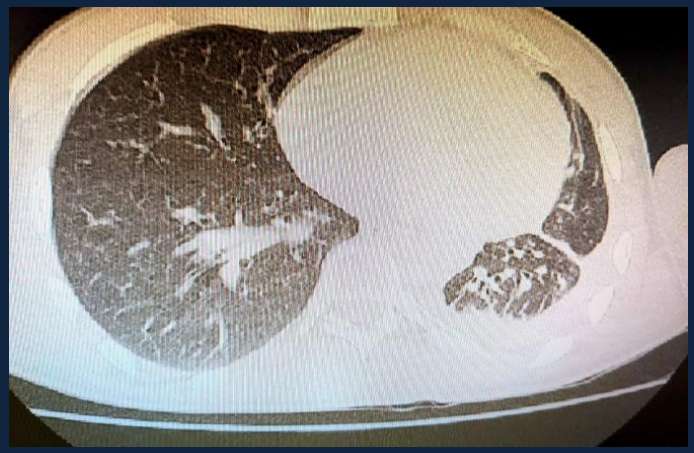






Lésions disséminées infra+ supra tentorielles, hyperT2, cocarde, atteinte tronc cérébral, non accessibles ponction





Des idées?

EVOLUTION USI

- Transfert USI sous CEFTRIAXONE 2GX2 + AMOXICILLINE 200mg/kg
- Crise convulsive généralisée le 13/02 : IOT et transfert Réanimation, DEPAKINE
- EEG : dysrythmie sans foyer, pas d'état de mal
- Nouvelle PL: très peu de liquide..

- PCR BK +, culture BK -
- Biopsie adp rétropéritonéale : PCR BK+
- ECBC BK négatifs, PCR BK+

PRISE EN CHARGE

- Introduction quadrithérapie 15/02/24:
  1. RIFAMPICINE 900mg/J
  2. PYRAZINAMIDE 1500mg/J
  3. ISONIAZIDE 300mg/J
  4. ETHAMBUTOL 800mg/J

- Corticothérapie SOLUMEDROL 1mg/kg

- Transfert Neurologie après extubation

EVOLUTION NEUROLOGIE

- PNP ttt/ TAZOCILLINE
- Cytolyse <3N résolutive
- Amélioration neurologique
- IRM cérébral contrôle : régression lésions
- Passage bithérapie po RIFAMP+ INH à 2 mois, durée totale prévue 12 mois

- Transfert SSR neuro 03/04, évolution favorable

TUBERCULOSE NEURO MENINGEE

1. Méningite tuberculeuse

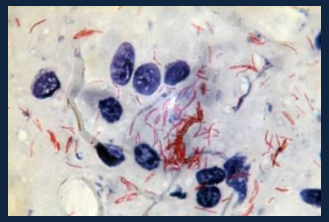
2. Tuberculome

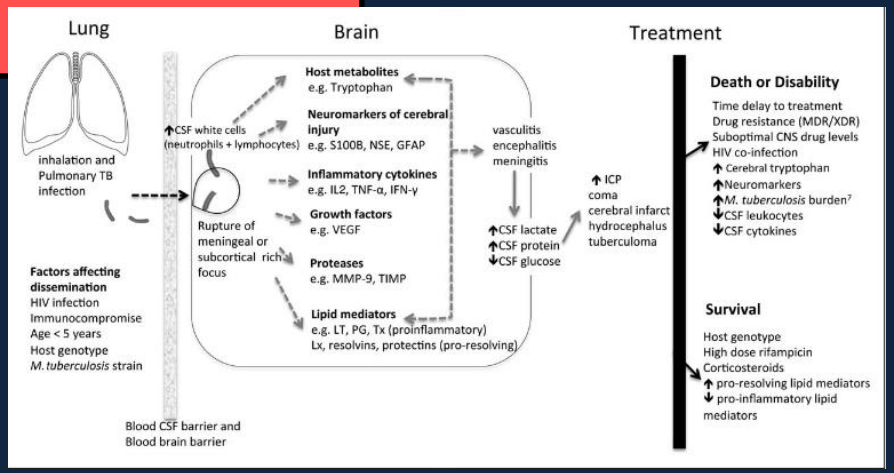
3. Arachnoidite spinale

4. Myélite transverse

1 - 5% des cas des TM
Sex ratio? 20-40 ans
VIH++
Morbi-mortalité (adulte 50%, enft 20%)
Associations possibles
Difficultés diagnostiques/pauci bacillaires

Physiopathologie: hématogène, exsudat gélatineux, vascularite, hydrocéphalie





Dastur et al., 1995 ; Donovan et al., 2020 ; Taous et al., 2022

1/ Méningite tuberculeuse

- Atteinte nerfs crâniens (III, VI)

- LCR :
  - Pleiocytose 100-500/yl, lymphocytes… PNN.. (stade précoce, atteinte médullaire, réaction paradoxale)
  - Hyperprotéinorachie (100-500 mg/dl)
  - Hypoglycorachie (<45mg/L)
  - Sens ED/BAAR 30-60%, culture BK <50%
  - PCR ++ (spe 99%/sens 82%) Xpert MTB/RIF Ultra
  - Lipoarabinomannane (LAM)? VIH
  - Adénosine désaminase ? Pleurésies

Analyse du LCR	Résultats (cas)
Aspect macroscopique	Clair dans 95% (20 cas)
Cytologie	≥ 5 GB/mm^3: 95% (20 cas)
	≤ 05 GB/mm^3: 4,8% (1 cas)
Formule	Prédominance lymphocytaire: 90% (18 cas)
	Prédominance PNN: 10% (2 cas)
Protéinorachie	≥ 0,3g/l: 10% (2 cas)
	≤ 0,3g/l: 20% (4 cas)
	≥ 1g/l: 70% (14 cas)
Glycorachie	≥ 0,5g/l: 14,3% (3 cas)
	≤ 0,5 g/l: 85,7% (18 cas)
Recherche de BK	Examen direct: positif dans un cas
	Culture: positive 1 cas
	PCR: positive 6 cas

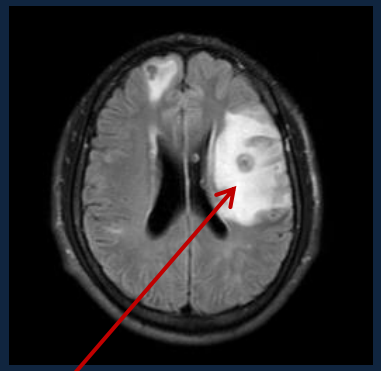
- Imagerie : leptoméningite

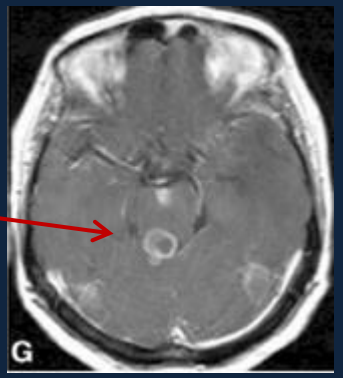
- Complications : AVC (26%), épilepsie (focale), hydrocéphalie (80% : TDM avant PL), hyponatrémie (SIADH), atteinte visuelle, myélite transverse

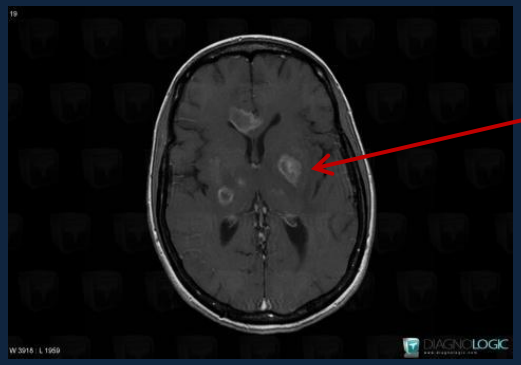
Taous et al.,2022 ; Donovan et al., 2020. Wasay et al., 2014 ; Chan et al., 2005 ; Ye et al., 2023 ; WHO 2017

2/ Tuberculome

- Conglomérat granulomateux
- Cérébral, médullaire
- Asymptomatique
- IRM ++ : hypoT1 hyperT2, cocarde
- Diagnostics différentiels:







Neurocysticercose (scolex…)
Cryptococcose
Toxoplasmose
Abcès cérébraux
Lymphome
Tumeur

Leonard et al., 2017 ; Wasay et al., 2014

3/ Arachnoidite spinale

- Lombosacrée > thoracique > cervicale
- Radiculonévrite ascendante, transverse
- Radiculalgie, dysesthésie, paralysie motoneurone, troubles sphinctériens
- Atteinte unique, multiple
- IRM, PL
- DD : tuberculome médullaire, spondylite-ostéomyélite /Pott, atteinte CMV (VIH), syphilis

Gard et al., 2015

4/ Myélite transverse

- Para/quadriparésie
- IRM, PL

TRAITEMENT (hors neurochirurgie)

- Empirique sans délai
- Quadrithérapie 2 mois puis bithérapie, durée totale 9-12 mois
  - ISONIAZIDE + RIFAMPICINE (dose??) + PYRAZINAMIDE + ETHAMBUTOL? ETHIONAMIDE/STREPTOMYCINE chez enfant
- Schéma court/quadrithérapie 6 mois chez enfant? Séquelles?
- Souches INH R : Fquinolone, MDR : 5 molécules (LEVO, ETHIONAMIDE/CYCLOSERINE, LINEZOLIDE, PYRAZINAMIDE, KANAMYCINE) BEDAQUILINE?? CLOFAMIZINE??, durée 18-24 mois
- VIH : délai 2 mois/IRIS
- Corticothérapie

ATS-CDC-IDSA/ British Society Guidelines/ WHO Guidelines

Forte dose de RIFAMPICINE ? Oui !

Randomized Clinical Trial of High-Dose Rifampicin With or Without Levofloxacin Versus Standard of Care for Pediatric Tuberculous Meningitis: The TBM-KIDS Trial

Mandar S. Paradkar,[1,2] Bella Devaleenal D.,[3] Tisungane Mvalo,[4,5] Ana Arenivas,[6] Kiran T. Thakur,[7] Lisa Wolf,[8] Smita Nimkar,[1,2] Sadaf Inamdar,[1,2] Prathiksha Giridharan,[3] Ellarasi Selladurai,[3] Aarti Kinikar,[1,10] Chhaya Valvi,[1,10] Saltanat Khwaja,[1,2] Daphne Gadama,[3] Sarath Balaji,[3] Krishna Yadav Kattagori,[3] Mythily Venkatesan,[3] Radojka Savic,[11] Soumya Swaminathan,[12] Amita Gupta,[6,7] Nikhil Gupte,[1,2,9] Vidya Mave,[1,2,9] and Kelly E. Dooley[8]; for the TuBerculous Meningitis in Kids (TBM-KIDS) Study Team

[1]ICJ Government Medical College–Johns Hopkins Clinical Research Site, Pune, India; [2]Johns Hopkins India, Pune, India; [3]Department of Clinical Research, Indian Council of Medical Research–National Institute for Research in Tuberculosis, Chennai, India; [4]UNC Project Malawi, Lilongwe, Malawi; [5]Department of Pediatrics, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [6]Section of Neuropsychology, Neurological Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA; [7]Department of Neurology, Columbia University Irving Medical Center/New York Presbyterian Hospital, New York, New York, USA; [8]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [9]Institute of Child Health and Hospital for Children, Chennai, India; [10]Department of Pediatrics, ICJ Government Medical College, Pune, India; [11]Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, California, USA; and [12]World Health Organization, Geneva, Switzerland

Background. Pediatric tuberculous meningitis (TBM) commonly causes death or disability. In adults, high-dose rifampicin may reduce mortality. The role of fluoroquinolones remains unclear. There have been no antimicrobial treatment trials for pediatric TBM.

Methods. TBM-KIDS was a phase 2 open-label randomized trial among children with TBM in India and Malawi. Participants received isoniazid and pyrazinamide plus: (*i*) high-dose rifampicin (30 mg/kg) and ethambutol (R_2HZE, arm 1); (*ii*) high-dose rifampicin and levofloxacin (R_2HZL, arm 2); or (*iii*) standard-dose rifampicin and ethambutol (R_1HZE, arm 3) for 8 weeks, followed by 10 months of standard treatment. Functional and neurocognitive outcomes were measured longitudinally using Modified Rankin Scale (MRS) and Mullen Scales of Early Learning (MSEL).

Results. Of 2487 children prescreened, 79 were screened and 37 enrolled. Median age was 72 months; 49%, 43%, and 8% had stage I, II, and III disease, respectively. Grade 3 or higher adverse events occurred in 58%, 55%, and 36% of children in arms 1, 2, and 3, with 1 death (arm 1) and 6 early treatment discontinuations (4 in arm 1, 1 each in arms 2 and 3). By week 8, all children recovered to MRS score of 0 or 1. Average MSEL scores were significantly better in arm 1 than arm 3 in fine motor, receptive language, and expressive language domains ($P < .01$).

Conclusions. In a pediatric TBM trial, functional outcomes were excellent overall. The trend toward higher frequency of adverse events but better neurocognitive outcomes in children receiving high-dose rifampicin requires confirmation in a larger trial.

Clinical Trials Registration. NCT02958709.

Keywords. pediatric tuberculous meningitis; neuropsychological; clinical trial; levofloxacin; high-dose rifampicin.

High-Dose Oral and Intravenous Rifampicin for the Treatment of Tuberculous Meningitis in Predominantly Human Immunodeficiency Virus (HIV)-Positive Ugandan Adults: A Phase II Open-Label Randomized Controlled Trial

Fiona V. Cresswell,[1,2,3] David B. Meya,[2] Enock Kagimu,[2] Daniel Grint,[4] Lindsey te Brake,[5] John Kasibante,[2] Emily Martyn,[1] Morris Rutakingirwa,[2] Carson M. Quinn,[6] Micheal Okirwoth,[2] Lillian Tugume,[2] Kenneth Ssembambulidde,[2] Abdu K. Musubire,[2] Ananta S. Bangdiwala,[7] Allan Buzibye,[2] Conrad Muzoora,[8] Elin M. Svensson,[5,9] Rob Aarnoutse,[5] David R. Boulware,[10,a] and Alison M. Elliott[1,3,a]

Conclusions. Current international guidelines result in sub-therapeutic CSF rifampicin concentration for 89% of Ugandan TBM patients. High-dose intravenous and oral rifampicin were safe and respectively resulted in exposures ~6- and ~8-fold higher than standard of care, and CSF levels above the MIC.

Meta-Analysis › Clin Infect Dis. 2020 Nov 5;71(8):1817-1823. doi: 10.1093/cid/ciz1071.

Model–Based Meta–analysis of Rifampicin Exposure and Mortality in Indonesian Tuberculous Meningitis Trials

Elin M Svensson [1 2], Sofiati Dian [3 4], Lindsey Te Brake [1], Ahmad Rizal Ganiem [3 4], Vycke Yunivita [4 5], Arjan van Laarhoven [6], Reinout Van Crevel [6], Rovina Ruslami [4 5], Rob E Aarnoutse [1]

Conclusions: Higher rifampicin exposure substantially decreased the risk of death, and the maximal effect was not reached within the studied range. We suggest a rifampicin dose of at least 30 mg/kg to be investigated in phase 3 clinical trials.

Randomized Controlled Trial › Clin Infect Dis. 2017 Jul 1;65(1):20-28. doi: 10.1093/cid/cix230.

Clinical Outcomes of Patients With Drug–Resistant Tuberculous Meningitis Treated With an Intensified Antituberculosis Regimen

A Dorothee Heemskerk [1 2], Mai Thi Hoang Nguyen [1], Ha Thi Minh Dang [1 3], Chau Van Vinh Nguyen [1 4], Lan Huu Nguyen [3], Thu Dang Anh Do [1], Thuong Thuy Thuong Nguyen [1], Marcel Wolbers [1 2], Jeremy Day [1 2], Thao Thi Phuong Le [1], Bang Duc Nguyen [1 3], Maxine Caws [1 5], Guy E Thwaites [1 2]

Conclusions: Early intensified treatment improved survival in patients with INH-R TBM. Targeted regimens for drug-resistant TBM should be further explored.

Forte dose de RIFAMPICINE ? Non !

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

Authors: A. Dorothee Heemskerk, M.D., Nguyen D. Bang, Ph.D., Nguyen T.H. Mai, Ph.D., Tran T.H. Chau, Ph.D., Nguyen H. Phu, Ph.D., Pham P. Loc, M.D., Nguyen V.V. Chau, Ph.D., +16, and Jeremy J. Farrar, F.R.C.P. Author Info & Affiliations

Published January 14, 2016 | N Engl J Med 2016;374:124-134 | DOI: 10.1056/NEJMoa1507062 | VOL. 374 NO. 2

CONCLUSIONS

Intensified antituberculosis treatment was not associated with a higher rate of survival among patients with tuberculous meningitis than standard treatment. (Funded by the Wellcome Trust and the Li Ka Shing Foundation; Current Controlled Trials number, ISRCTN61649292.)

Review > J Clin Pharm Ther. 2022 Apr;47(4):445-454. doi: 10.1111/jcpt.13555. Epub 2021 Dec 12.

High-dose rifampicin for the treatment of tuberculous meningitis: a meta-analysis of randomized controlled trials

Yan Cao [1], Tao Wang [1], Ke He [1], Juanmin Xue [1], Xinjing Wang [1], Jianqin Liang [1]

What is new and conclusion: High-dose rifampicin was not a protective factor for 6-month mortality, despite increased plasma C_{max} and AUC_{0-24h}. However, the above conclusions are still required to be verified through more RCTs due to the limited quantity of included studies.

Meta-Analysis > Int J Mycobacteriol. 2021 Jul-Sep;10(3):312-319. doi: 10.4103/ijmy.ijmy_135_21.

Safety and efficacy of high-dose rifampicin in the management of tuberculosis meningitis: Systematic review and meta-analysis

Loveness Charlie [1], Solomon Mequante Abay [2], Abraham Tesfaye [1], Ronald Nachipo Mlera [3], Samuel Mwango [4], Mary Goretti [5]

Conclusions: It can be concluded from this meta-analysis that there is no significant relation of high-dose rifampicin with adverse events and the reduction of mortality in TBM patients. Whether in future optimized TBM treatment regimen will include high-dose rifampicin or not should be determined by a large-scale clinical trial.

Corticothérapie :

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

Authors: Guy E. Thwaites, M.R.C.P., Nguyen Duc Bang, M.D., Nguyen Huy Dung, M.D., Hoang Thi Quy, M.D., Do Thi Tuong Oanh, M.D., Nguyen Thi Cam Thoa, M.D., Nguyen Quang Hien, M.D., +13, and Jeremy J. Farrar, F.R.C.P. Author Info & Affiliations

Published October 21, 2004 | N Engl J Med 2004;351:1741-1751 | DOI: 10.1056/NEJMoa040573 | VOL. 351 NO. 17

Review › Cochrane Database Syst Rev. 2016 Apr 28;4(4):CD002244.
doi: 10.1002/14651858.CD002244.pub4.

Corticosteroids for managing tuberculous meningitis

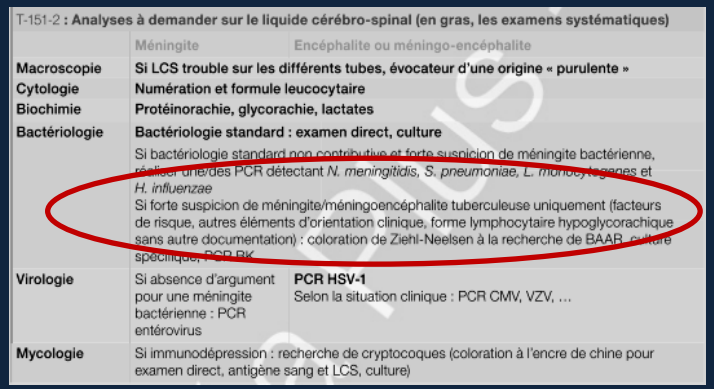
Kameshwar Prasad [1], Mamta B Singh, Hannah Ryan

- 0.4 mg/Kg/j puis décroissance sur 6-8 semaines
- 0.6 mg/Kg/j chez enfant < 14 ans
- DEXAMETHASONE ou PREDNISOLONE (0.5 mg/kg/J)
- Indications neuro BK
  - Méningite BK, VIH -/VIH +
  - Tuberculome avec œdème/hydrocéphalie
  - Arachnoidite spinale sévère (protéinorachie>500mg/dL), compression
  - Myélite transverse

British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children; WHO 2017 ; Central Nervous System Tuberculosis , Microbiol Spectr, 2017

CONCLUSION

- Mr M: Tuberculose neuro-méningée avec tuberculomes, crise convulsive généralisée, SIADH sur atteinte centrale, méningite prédominance PNN!! : attention aux associations, et aux dogmes..
- Morbi-mortalité lourde
- Difficultés diagnostiques, PCR ++
- TDMc, PL, IRMc
- Quadrithérapie initiale 2 mois, durée totale 9-12 mois
- Dose RIFAMPICINE? Dosage ?
- Place Quinolones?
- Corticothérapie



T-151-2 : **Analyses à demander sur le liquide cérébro-spinal (en gras, les examens systématiques)**

	Méningite	Encéphalite ou méningo-encéphalite
Macroscopie	**Si LCS trouble sur les différents tubes, évocateur d'une origine « purulente »**	
Cytologie	**Numération et formule leucocytaire**	
Biochimie	**Protéinorachie, glycorachie, lactates**	
Bactériologie	**Bactériologie standard : examen direct, culture** Si bactériologie standard non contributive et forte suspicion de méningite bactérienne, réaliser une/des PCR détectant *N. meningitidis*, *S. pneumoniae*, *L. monocytogenes* et *H. influenzae* Si forte suspicion de méningite/méningoencéphalite tuberculeuse uniquement (facteurs de risque, autres éléments d'orientation clinique, forme lymphocytaire hypoglycorachique sans autre documentation) : coloration de Ziehl-Neelsen à la recherche de BAAR, culture spécifique, PCR BK	
Virologie	Si absence d'argument pour une méningite bactérienne : PCR entérovirus	**PCR HSV-1** Selon la situation clinique : PCR CMV, VZV, …
Mycologie	Si immunodépression : recherche de cryptocoques (coloration à l'encre de chine pour examen direct, antigène sang et LCS, culture)	

Pilly 2023 item 151

Merci