

The use of Thalidomide in childhood TB meningitis

Johan Schoeman

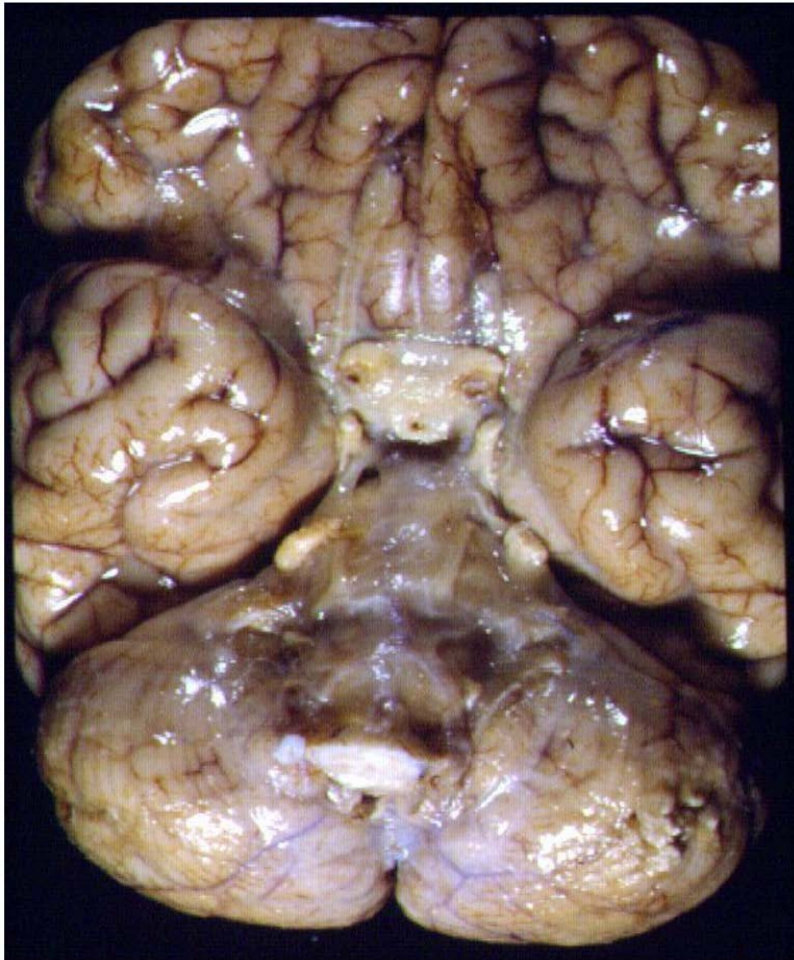
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Cape Town, South Africa





Macro-pathology in TBM



Why the need for Thalidomide as adjuvant in TB meningitis?

- Evidence of on-going inflammatory response.
- Inflammatory response immunologically mediated
- Significant mortality and morbidity in spite of effective antituberculosis drugs
- Corticosteroids: reduce mortality, not morbidity

– Schoeman et al Pediatrics 1997; 99: 226-231

– Thwaites et al N Engl J Med 2004; 351: 1741-51

Experimental studies: Thalidomide rabbit model TBM

- **Thalidomide**

- Reduction CSF cells, less pathology, improved survival
- Reduced CSF TNF-alpha

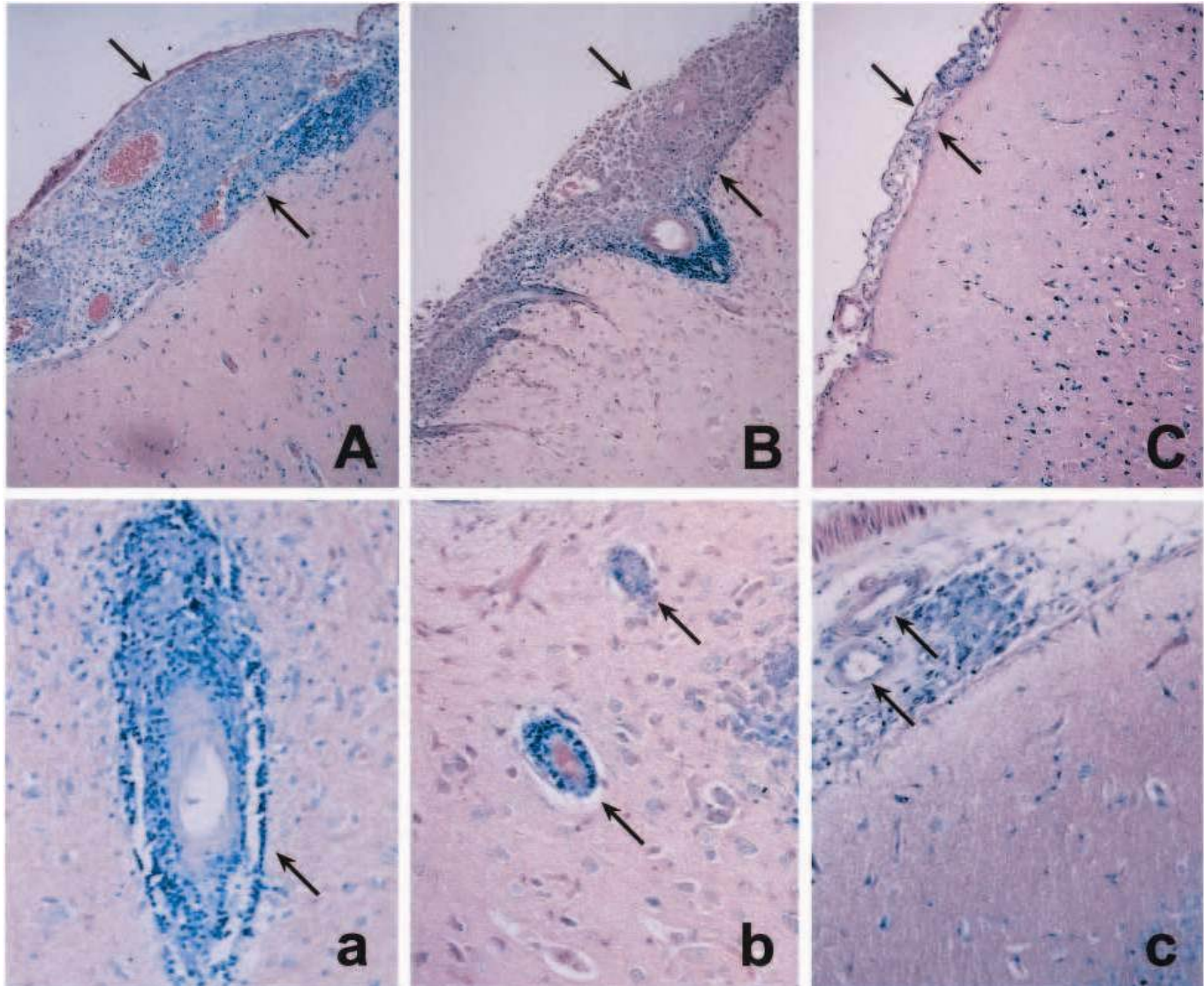
– Tsenova et al. J Infect Dis 1998; 177: 1563

- **Thalidomide analog (IMiD3)**

- Improves survival to 75% (thalidomide 50%)
- Excellent pharmacokinetic profile CSF
- No teratogenicity in rabbits

– Tsenova et al. Antimicrobial agents and Chemotherapy 2002; June:
1887-1895

Thalidomide analogue: IMiD3: Role in experimental TBM



Use of thalidomide in TB meningitis

Adjunctive Thalidomide Therapy of Childhood Tuberculous Meningitis: Possible Anti-Inflammatory Role

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ABSTRACT

Pilot study

- **Methods**

- 15 patients stage 2 TBM: dose-escalating, safety, pilot study

- **Results**

- Basal enhancement: absent in all
- Tuberculomas: resolved; no new
- Infarcts: smaller
no new lesions
- Hemiplegia: possibly better outcome than historical controls
- Decrease in serum and CSF TNF-alpha

Adjunctive Thalidomide Therapy for Childhood Tuberculous Meningitis: Results of a Randomized Study

Johan F. Schoeman, MBChB, MD; Priscilla Springer, MBChB, FCP; Anita Janse van Rensburg, Dipl Nurs; Sonja Swanevelder, MSc; Willem A Hanekom, MBChB, FCP; Patrick A. J. Haslett, MB, MRCP; Gilla Kaplan, PhD

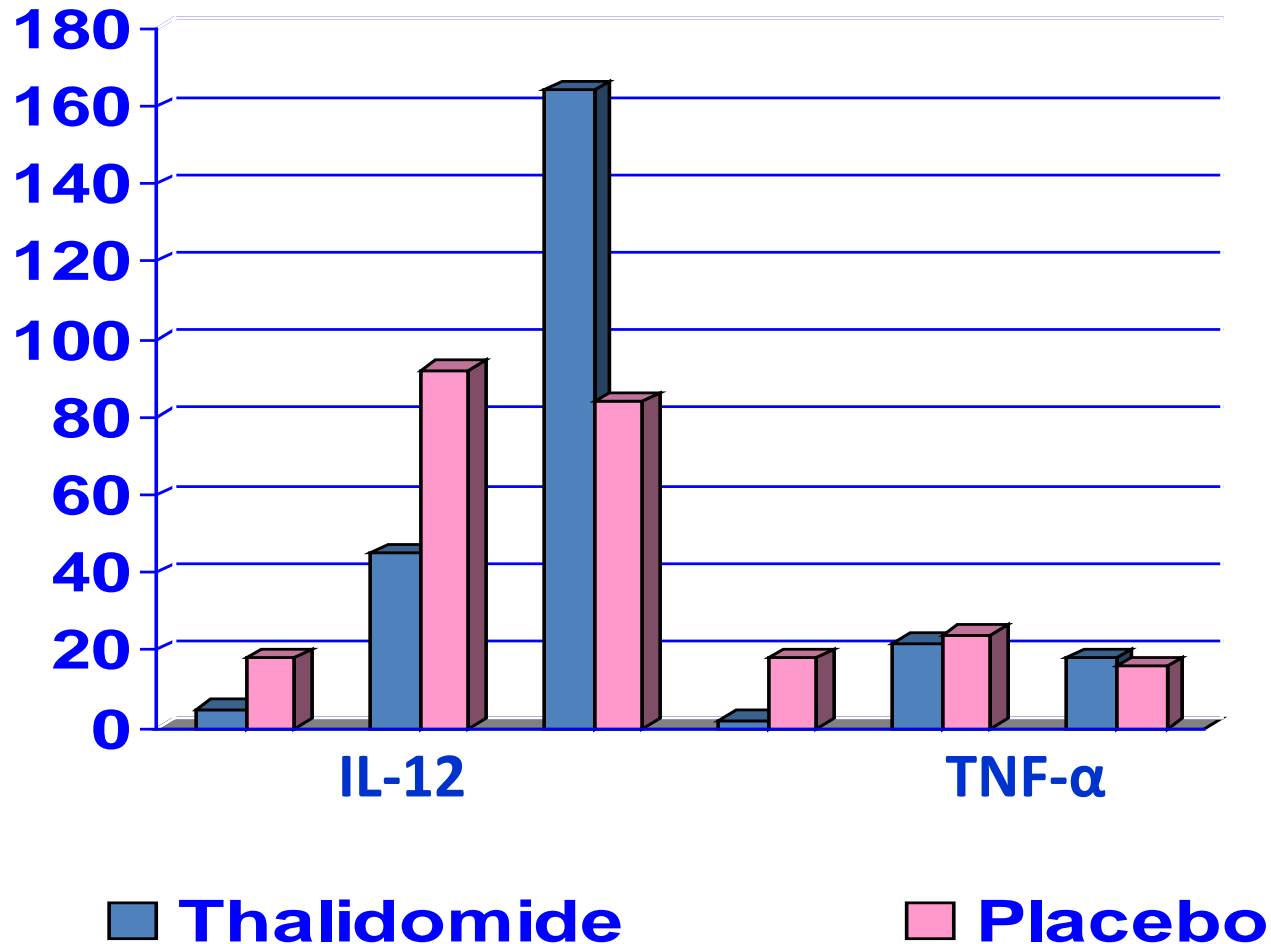
ABSTRACT

Childhood tuberculous meningitis is associated with serious long-term sequelae, including mental retardation, behavior disturbances, and motor handicap. Brain damage in tuberculous meningitis results from a cytokine-mediated inflammatory response, which causes vasculitis and obstructive hydrocephalus. Thalidomide, a potent tumor necrosis factor α

Double-blind randomized study (47 patients)

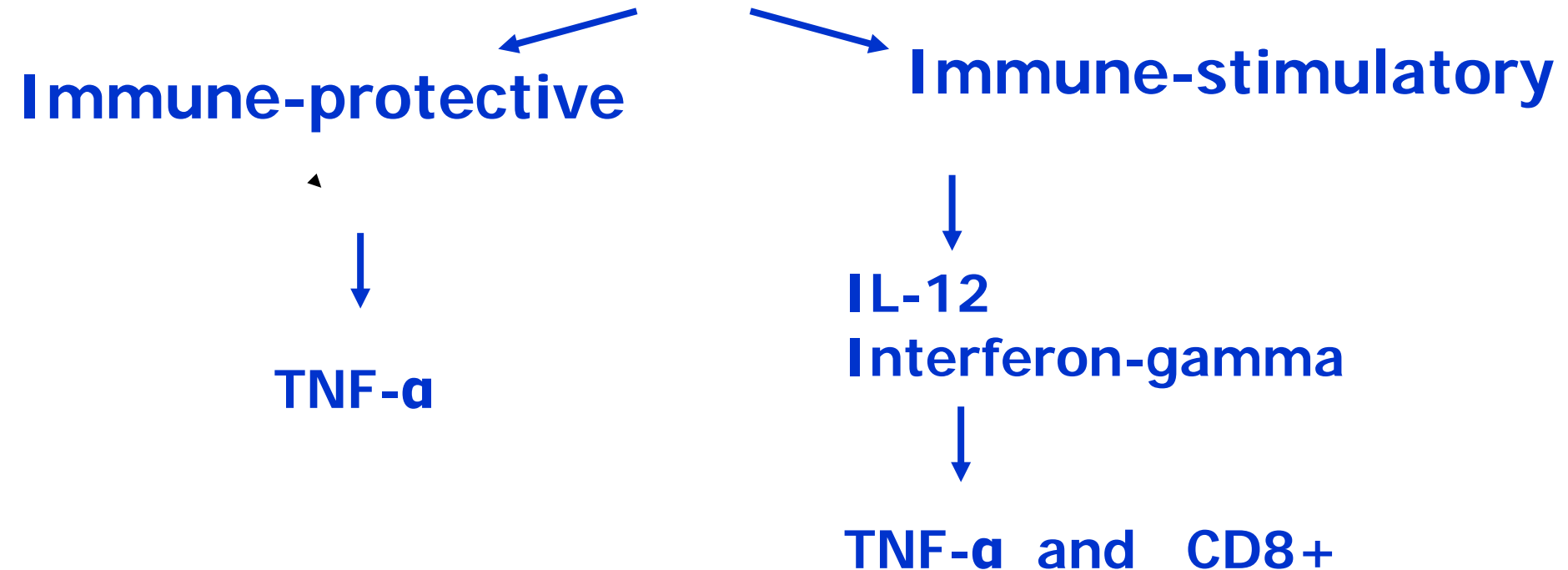
- Side-effects:
 - Skin rash (20%)
 - Hepatitis (26%)
 - Neutropaenia/thrombocytopaenia (6%)
- Deaths:
 - 4 patients (17%)
- Clinical outcome

Results: cytokines plasma and CSF



Discussion: possible mechanism of action of thalidomide

THALIDOMIDE

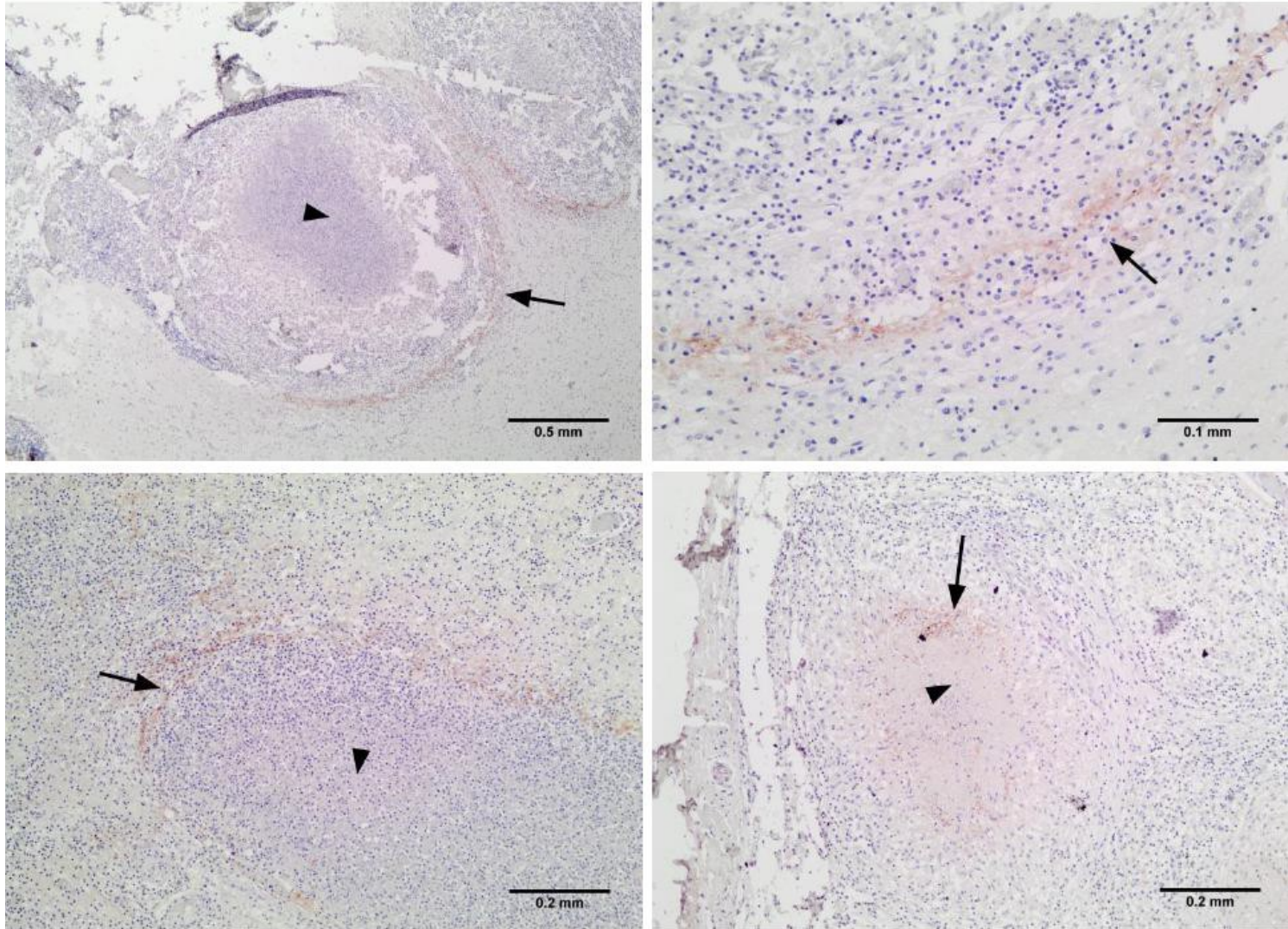


Thalidomide: other evidence of immune-stimulation

- **Thalidomide causes immune-stimulation in patients with HIV and TB**
 - Linda-Gail Bekker et al. J inf Dis 2000; 181:954-965
- **Effective treatment of erythema nodosum leprosum with thalidomide is associated with immune stimulation**
 - Haslett PA et al. J Infect Dis 2005; 192:2045-2053
 - TNF- α unchanged or increased
 - Increased interferon-gamma and IL 12
 - Increased CD4 and CD8 cells

Use of thalidomide in intracranial TB mass lesions

TNF- α Immunostaining of a TB abscess



Courtesy : Zahari D

Original Article

Intractable Intracranial Tuberculous Infection Responsive to Thalidomide: Report of Four Cases

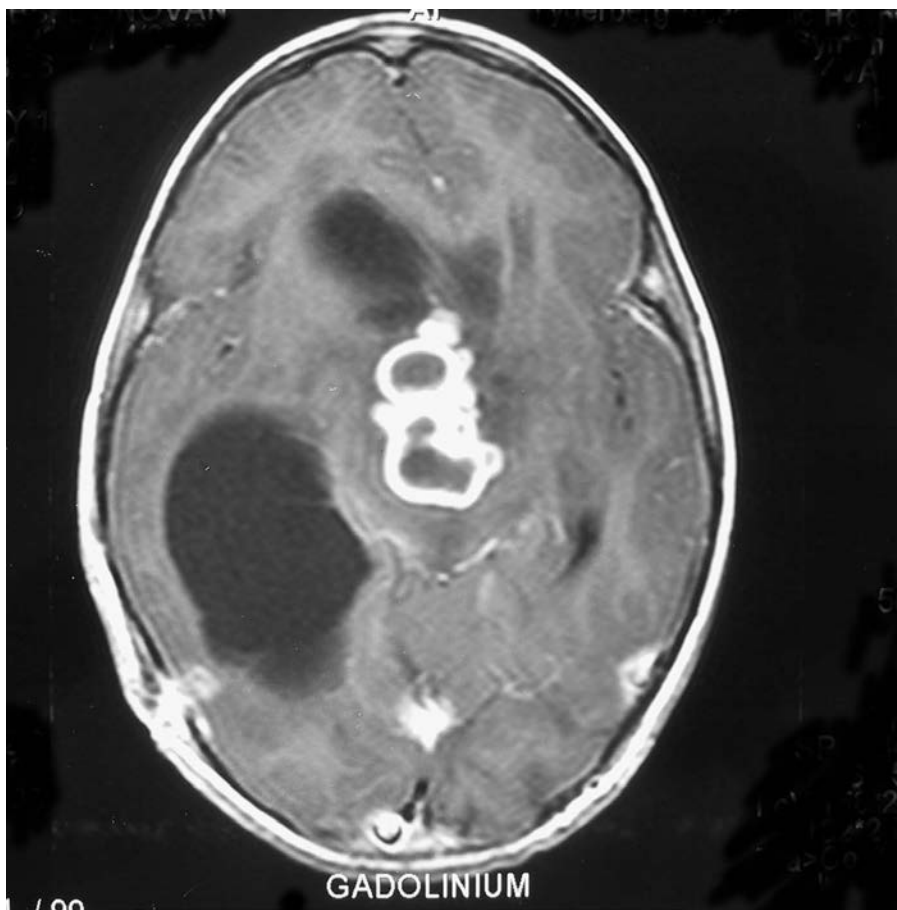
Johan F. Schoeman, MD; Graham Fieggen, FCS (SA); Neil Seller, FCPaed (SA); Marc Mendelson, PhD;
Bennie Hartzenberg, MMed (Neurosurg)

ABSTRACT

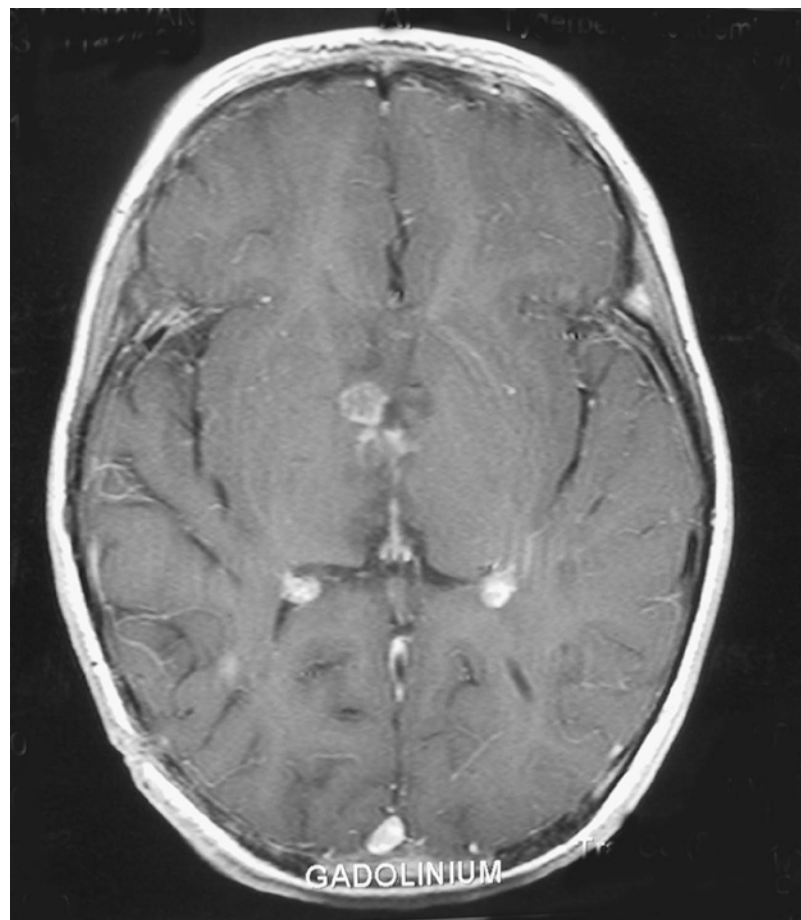
Paradoxical enlargement and development of new intracranial tuberculomas and tuberculous brain abscesses on adequate antituberculosis treatment are well recognized and supposedly cytokine mediated. These lesions are often unresponsive to conventional antituberculosis treatment, corticosteroids, and surgery. We therefore assessed the effect of adjunctive thalidomide, a tumor necrosis factor α -modulating drug, in intractable intracranial tuberculosis that did not respond to standard medical and surgical therapy. Four consecutive children (three children with bacteriologic proof and one child with clinical evidence of intracranial tuberculosis) were studied. Three patients each had a giant tuberculous abscess, and

Thalidomide: effect in intracranial TB abscess

- 5 consecutive cases of tuberculous abscess
- Intractable: no response to TB Rx, steroids and surgical drainage
- Dramatic clinical and MRI response to low dose (3-5 mg/kg/day) thalidomide
- Treated for 4-8 months
- No side-effects



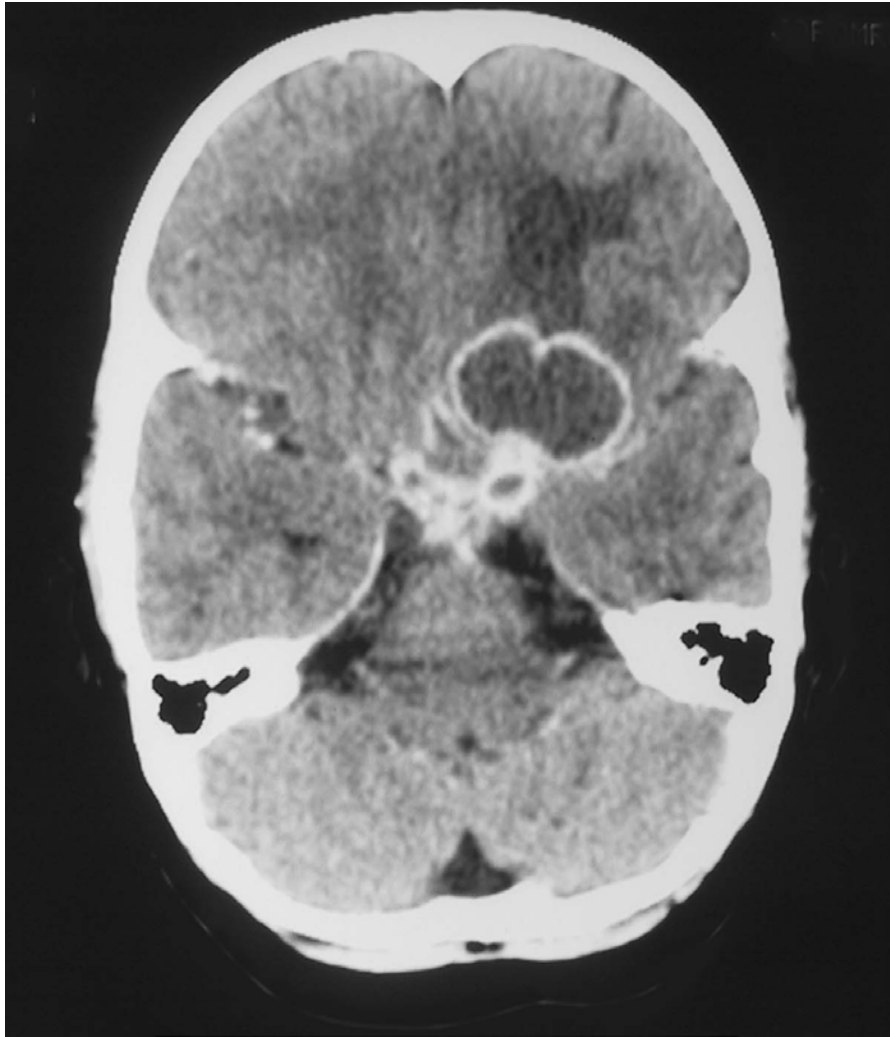
Before Thalidomide



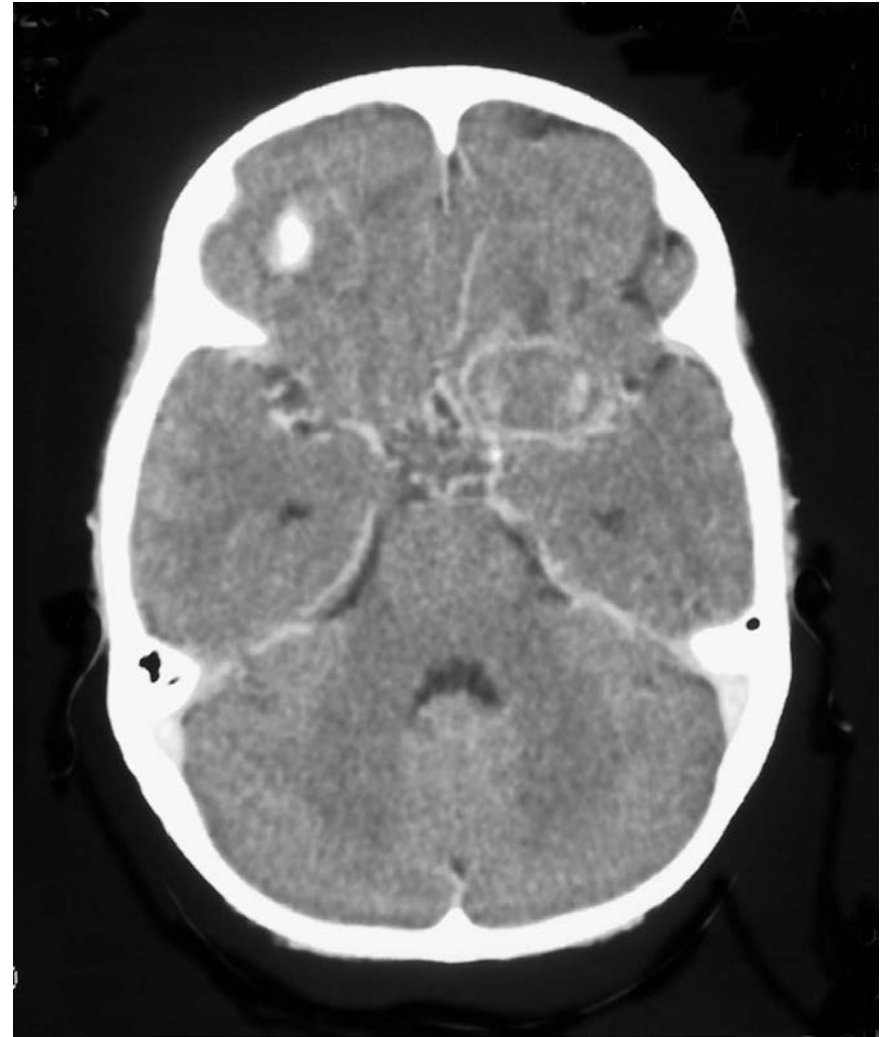
After Thalidomide



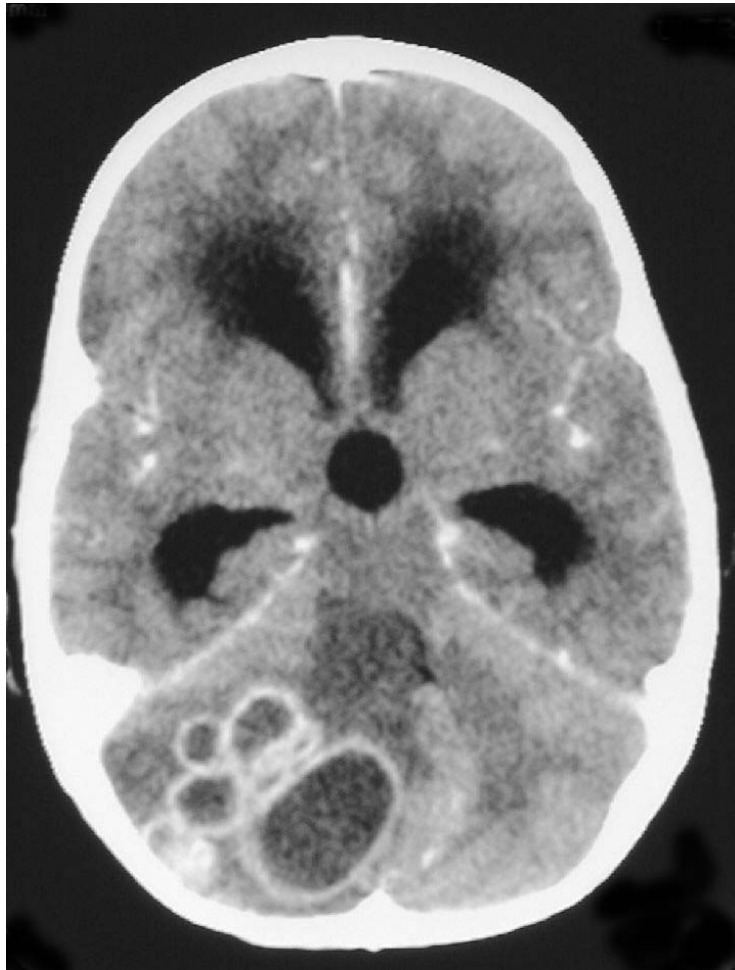




Before Thalidomide



After Thalidomide



Before Thalidomide



After Thalidomide

Epidural TB abscesses only responsive to Thalidomide



Demographics of 30 consecutive children with TB mass lesions treated with thalidomide

- 17 Male
- 8 HIV infected 22 HIV-uninfected
- Mean age 32 months (range 8-144 months)
- The mean duration for development of the TB mass lesion (paradoxical TB-IRIS) after initiation of anti-TB treatment was 3 months
- (range 0–5 months).
- HIV-related paradoxical TB-IRIS occurred within 2 months of antiretroviral therapy initiation in all of the HIV-infected children.

Clinical Response to Thalidomide therapy (n=30)

- Cessation of epilepsy partialis continua within 10 days of therapy (n=2)
- Resolution of ataxia within weeks (n=7)
- Recovery of walking in previously paraplegic children (n=2)
- Full recovery of vision in previously blind child (n=6)
- .
- Improvement of motor deficit (n=3). Full recovery of motor deficit (n=8)

Thalidomide adverse effects

- Skin rash
- Deranged liver enzymes
- Thrombocytopenia
Neutropenia
- Somnolence
- Peripheral neuropathy (sensorimotor axonal neuropathy)

None of our study children experienced any adverse effects.
Sural nerve action potentials proved normal in all 3 children with cumulative thalidomide dose larger than 20g.

2 other recent case reports

- **Multiple tuberculomas resistant to corticosteroids**
 - De la Riva et al. Neuropharmacol 2013; 36:70-72
- **Thalidomide in refractory tuberculoma and pseudoabscesses**
 - Viel-Theriault et al. Pediatr Infect Dis J 2016

Tuberculous Meningitis-Related Optic Neuritis: Recovery of Vision With Thalidomide in 4 Consecutive Cases

Journal of Child Neurology

25(7) 822-828

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Ronald van Toorn, FCP¹**

Abstract

Blindness is an uncommon but devastating complication of tuberculosis meningitis. The main causes are chronically raised intracranial pressure (hydrocephalus and/or tuberculomas) or direct involvement of the optic chiasm or optic nerves by the basal arachnoiditis (inflammation and/or compression). Antituberculosis therapy combined with corticosteroids and control of intracranial pressure constitutes the mainstay of therapy for tuberculous meningitis. Despite these treatment measures, some patients develop blindness, mainly as a result of progressive optochiasmatic arachnoiditis. This led us to explore the role of adjuvant thalidomide therapy, and we describe the dramatic recovery of vision in 4 consecutive cases. Clinical recovery was

Thalidomide: reverses blindness due to opto-chiasmatic tuberculous neuritis

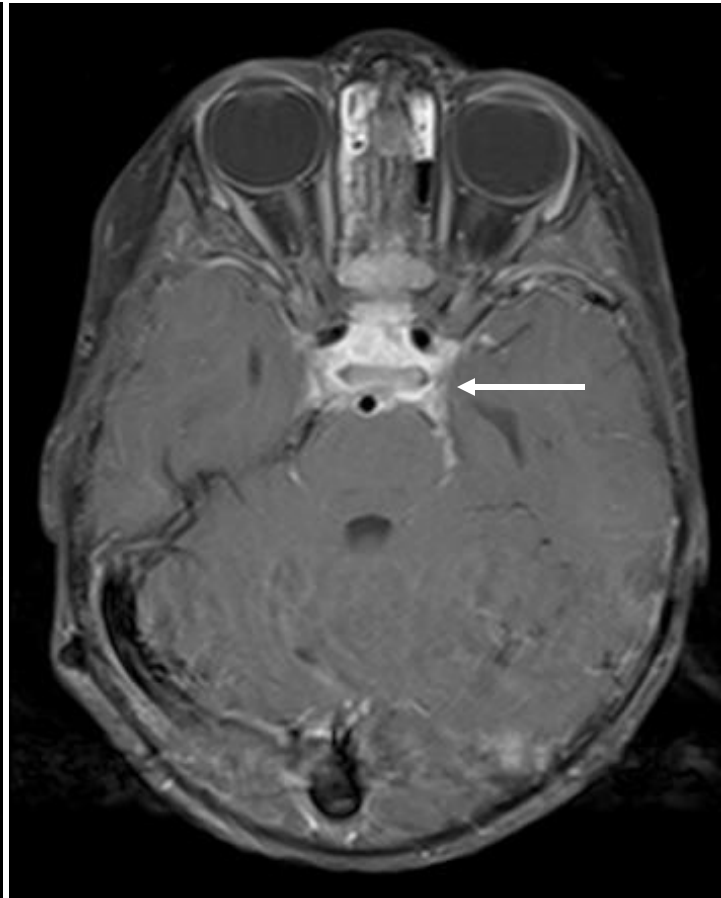
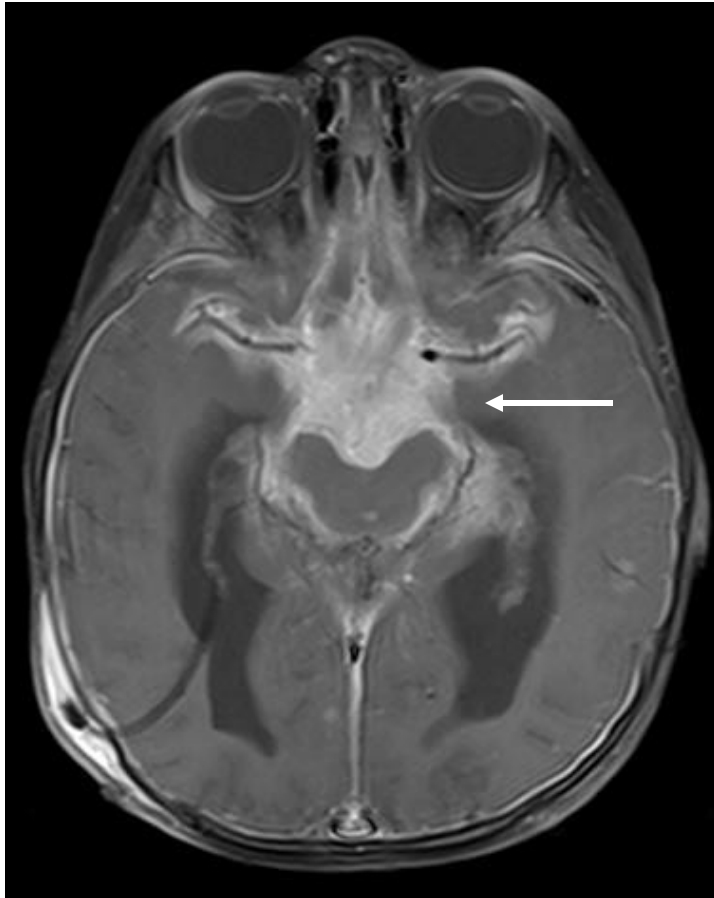
- 4 consecutive blind children
- Ophthalmologist confirms optic atrophy / absent pupil reflexes/ searching nystagmus
- Thalidomide 4-5 mg/kg/day for 3-8 months
- All recovered 6/6 vision and normal visual fields
- Corresponding MRI resolution of basal enhancement

Schoeman et al. J Child Neurol 2010;

Recovery of vision

Pre Thalidomide

Post Thalidomide



Schoeman JF et al J Child Neurology 2010

Clinicoradiologic Response of Neurologic Tuberculous Mass Lesions in Children Treated With Thalidomide

van Toorn, Ronald FCP^{*}; du Plessis, Anne-Marie FCRad[†]; Schaaf,
Hendrik Simon MD^{*}; Buys, Heliose FCP[‡]; Hewlett, Richard H.
PhD[§]; Schoeman, Johan F. MD^{*}

Pediatric Infectious Disease Journal: [February 2015 - Volume 34 -
Issue 2 - p 214–218](#)

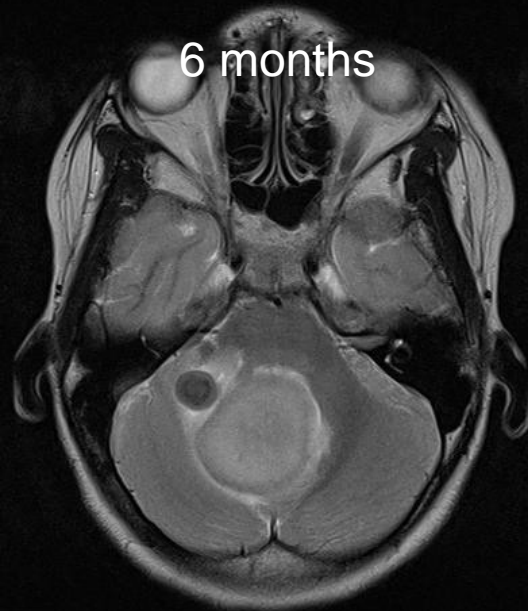
Pre treatment



3 months



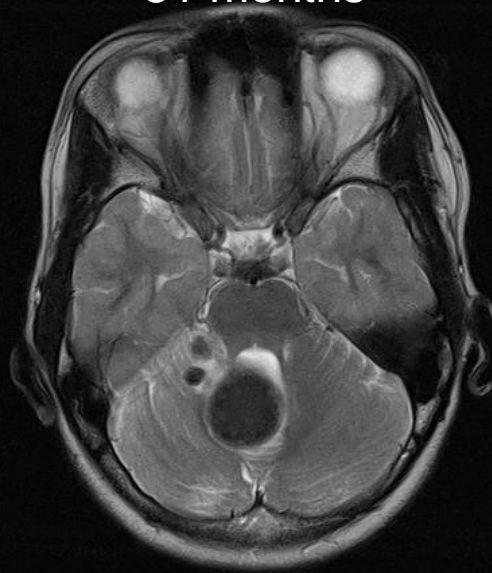
6 months



10 months



31 months



41 months



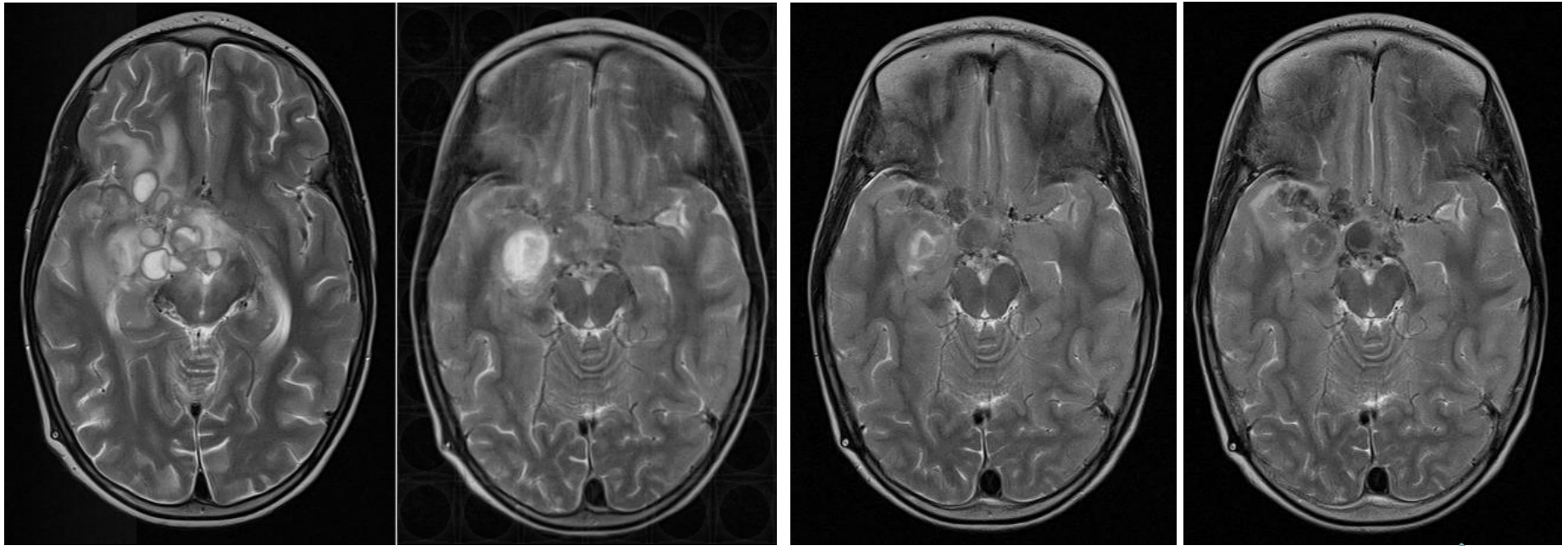
MRI T2 weighted imaging

Start treatment

3 months

6 months

11 months



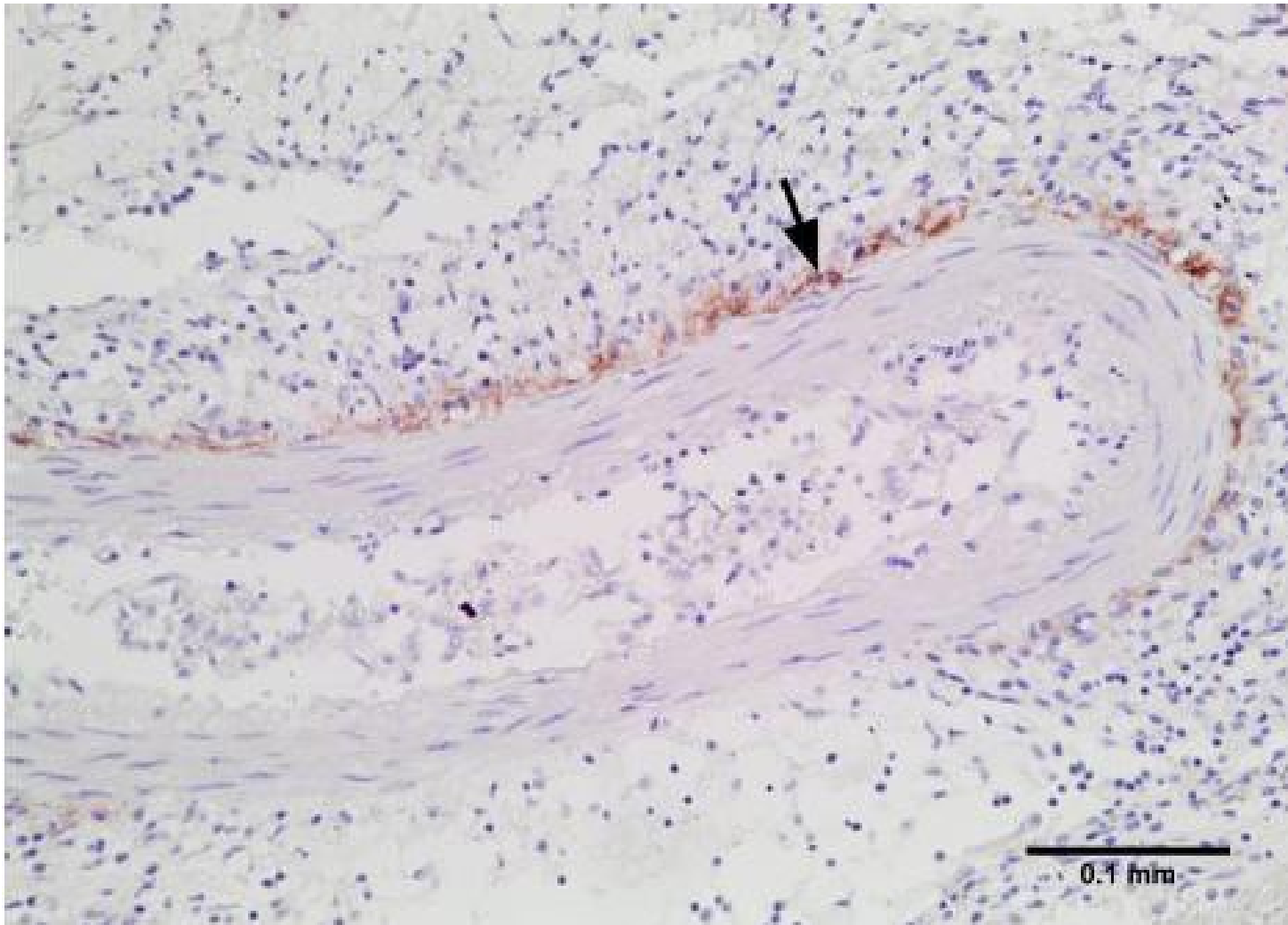
Asymptomatic

Stop Thalidomide

The possible role of Thalidomide in TB Vasculitis

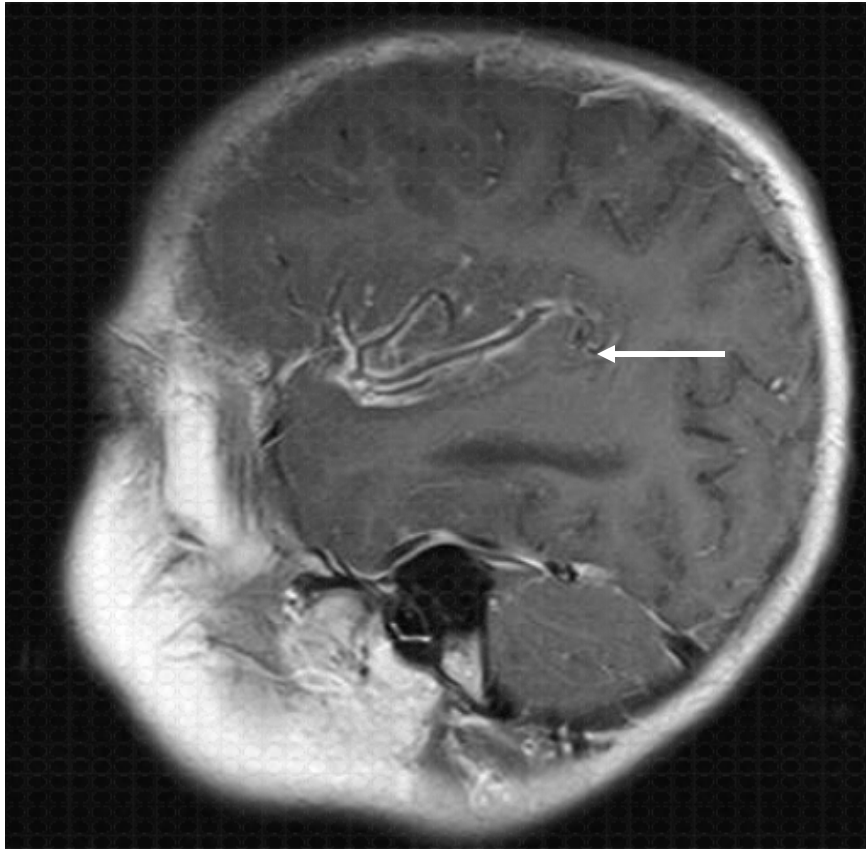
- Vascular endothelial growth factor (VEGF) is increased in CSF of TBM cases
 - Van der Vlier et al. *Pediatr Infect Dis J* 2004;23:608-13
- VEGF associated with cerebral infarction in TBM
 - Misra et al. *Int J Neurosci* 2013;123: 128-132
- VEGF strongly correlated with
 - CSF protein >1gm/L (p=.009)
 - Hydrocephalus (p=.001)
 - Basal enhancement and pre-contrast hyperdensity (p=.005 and .002)
 - Visser D et al. *Clin Infect Dis* 2015; 60:177-187
- Thalidomide ↓ VEGF both in vitro and in vivo and is anti angiogenic

Perivascular TNF- α staining

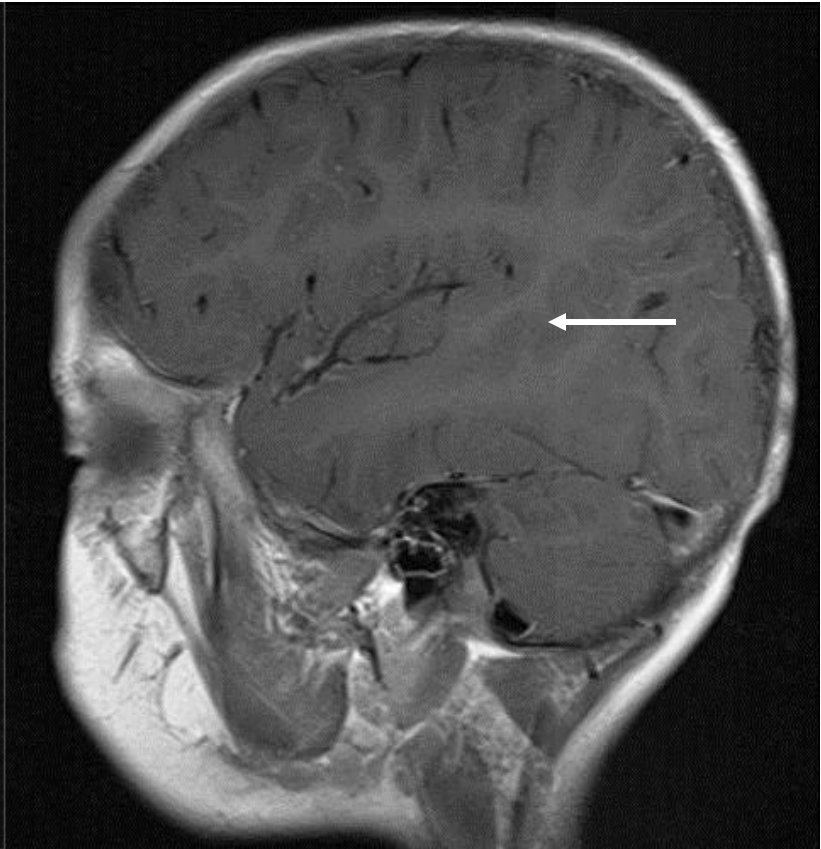


Courtesy : Zahari D

TBM-associated vasculitis



Pre Thalidomide



Post Thalidomide

Thalidomide in TBM

- Dose of thalidomide
 - Stage TBM
- Host genetics (hypo/hyper inflam)



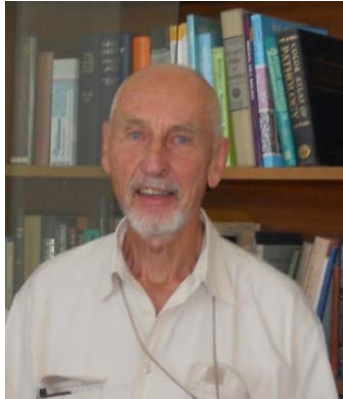
Clinical benefit

Adverse events

Conclusions

- Thalidomide has shown definite immune-modulatory effects in both experimental and clinical TB meningitis.
- The serious side-effects and possible deaths in Stage 3 TB meningitis most likely related to the high dose of thalidomide used and needs further investigation.
- Thalidomide has shown remarkable clinical and radiological improvement in a large series of consecutive intracranial and spinal TB mass lesions with minimal side-effects at low dose.

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Priscilla Springer