Infectious Diseases causing Seizures and/or Epilepsy

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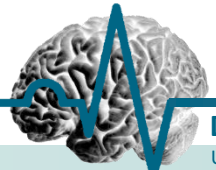
Department of Neurology – Division of Neurocritical Care
University Hospital Innsbruck, Austria



Published in final edited form as:
Lancet Neurol. 2014 October ; 13(10): 1029–1044. doi:10.1016/S1474-4422(14)70114-0.

Epidemiology, causes, and treatment of epilepsy in sub-Saharan Africa

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In short: in many parts of Africa: Infections are main cause of symptomatic/ secondary seizures

Neurological infections

Infectious causes that can lead to generalised seizures in equatorial Africa are mainly of parasitic origin. Among these conditions are malaria,88 cysticercosis, onchocerciasis, and toxocariasis.99

Neurocysticercosis is the most common neurological infection and a major cause of epilepsy in many countries in Africa, Asia, and Latin America.100–102 Neurocysticercosis is the main cause of partial epilepsy in adults in areas where *Taenia solium* is endemic. 101,103,104 Cysticercosis is not common in Jewish and Muslim countries (there is little contact between people and pigs, and pork is not eaten) because of the low risk of infection

neurocysticercosis, cerebral malaria, toxocarosis,
acute bacterial meningitis, viral encephalitis,
cerebral abscess, sub-, epidural empyema,
CNS tuberculosis (esp. tuberculomata)
febrile convulsions in early childhood

African countries found a significant association between cysticercosis and epilepsy (overall OR 3·4, 95% CI 2·7–4·3).104

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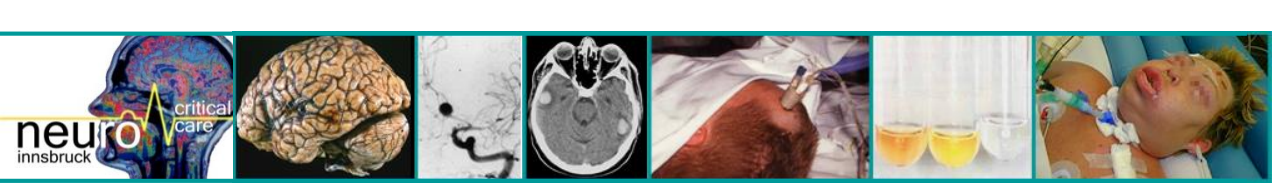

NEUROCYSTICERCOSIS AND OTHER HELMINTHIC DISEASES

ACUTE BACTERIAL MENINGITIS

BRAIN ABSCESS

ACUTE VIRAL ENCEPHALITIS

CHRONIC MENINGITIS INCL GRANULOMA (TB)

CEREBRAL MALARIA AND OTHER PROTOZOAL DISEASES

FREQUENT CAUSES OF

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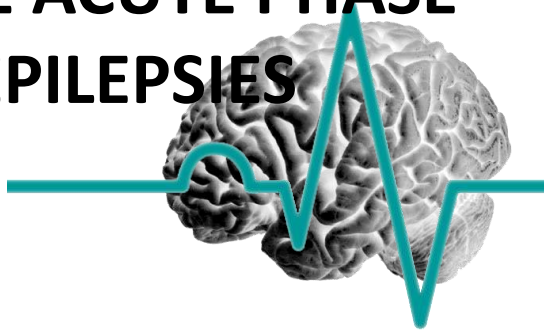
- SYMPTOMATIC POSTENCEPHALITIC EPILEPSIES



Epilepsia, 50(5):987–993, 2009
doi: 10.1111/j.1528-1167.2008.01867.x

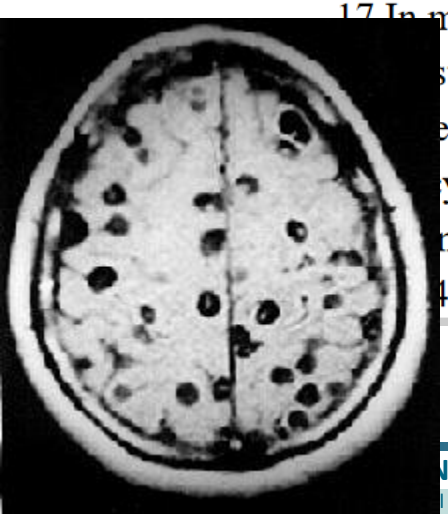
FULL-LENGTH ORIGINAL RESEARCH

Epilepsy and neurocysticercosis in rural Tanzania—An imaging study

*†[1]Andrea Sylvia Winkler, †‡[1]Joachim Blocher, §Herbert Auer, ¶Thaddaeus Gotwald, **William Matuja, and ‡Erich Schmutzhard

*Department of Neurology, Ludwig-Maximilians-University, Munich, Germany; †Haydom Lutheran Hospital, Manyara Region, Tanzania; ‡Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria; §Department of Medical Parasitology, Clinical Institute of Hygiene and Medical Microbiology, Medical University Vienna, Vienna, Austria; ¶Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria; and **Department of Neurology, Muhimbili National Hospital, Dar es Salaam, Tanzania

Africa, who were therefore at risk of developing epilepsy, was between 1·9 and 6·16 million.
17 In many resource-poor areas, with no access to neuroimaging, serological detection of
sticercal antibodies or cysticercal antigen is the method of choice to assess the
ence of human cysticercosis or neurocysticercosis.106 The prevalence of
ysticercosis varies throughout sub-Saharan Africa. A meta-analysis in 2010 on eight
n countries found a significant association between cysticercosis and epilepsy (overall
4, 95% CI 2·7–4·3).104



Lancet Infect Dis. 2014 August ; 14(8): 687–695. doi:10.1016/S1473-3099(14)70779-0.

Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial

Hector H Garcia, **Isidro Gonzales**, **Andres G Lescano**, **Javier A Bustos**, **Mirko Zimic**, **Diego Escalante**, **Herbert Saavedra**, **Martin Gavidia**, **Lourdes Rodriguez**, **Enrique Najar**, **Hugo Umeres**, **E Javier Pretell**, and **for The Cysticercosis Working Group in Peru**
Instituto Nacional de Ciencias Neurológicas, Lima, Peru (Prof H H Garcia PhD, I Gonzales MD, H Saavedra MD); Department of Microbiology (Prof H H Garcia, J A Bustos MD), Center for Global Health Tumbes (Prof H H Garcia), School of Public Health (A G Lescano PhD), and Bioinformatics Unit, Laboratory of Research and Development, School of Sciences and Philosophy (Prof M Zimic PhD), Universidad Peruana Cayetano Heredia, Lima, Peru; Department of Parasitology and Public Health Training Program, US Naval Medical Research Unit No 6 (NAMRU6), Callao, Peru (A G Lescano); Magnetic Resonance Imaging Center, Resocentro, Lima, Peru (D Escalante MD); Hospital Nacional Edgardo Rebagliati, Essalud, Lima, Peru (M Gavidia MD); Hospital Nacional Guillermo Almenara, Essalud, Lima, Peru (L Rodriguez MD); Hospital Nacional Cayetano Heredia, Ministerio de Salud, Lima, Peru (E Najar MD, H Umeres MD); and Hospital Nacional Alberto Sabogal, Essalud, Callao, Peru (E Javier Pretell MD)

Table 2

Cysticidal efficacy by treatment group and number of cysts

	Albendazole plus praziquantel (n=39)	Standard albendazole (n=41)	Increased albendazole (n=38)	Overall p value
One to two cysts				
Viable cysts at baseline	27	22	23	0·284
Mean per patient (SD)	1·4 (0·6)	1·1 (0·3)	1·3 (0·6)	0·281
Cyst range	1–3*	1–2	1–3*	..
Number of patients	20	20	18	..
Viable cysts at day 180	10	6	3	0·237
Mean per patient (SD)	0·5 (07)	0·3 (0·5)	0·2 (04)	0·162
Cysts resolved	17/27 (63%)	16/22 (73%)	20/23 (87%)	0·141
Patients cured	12/20 (60%)	14/20 (70%)	15/18 (83%)	0·287
Three or more cysts				
Viable cysts at baseline	171	142	142	0·179
Mean per patient (SD)	9·0 (4·8)	6·8 (4·2)	7·1 (44)	0·245
Cyst range	3–19	3–18	3–18	..
Number of patients	19	21	20	..
Viable cysts at day 180	11	112	74	<0·0001
Mean per patient (SD)	0·6 (1·0)	5·3 (4·2)	3·7 (3·1)	0·0001
Cysts resolved	160/171 (94%)	30/142 (21%)	68/142 (48%)	<0·0001
Patients cured	13/19 (68%)	1/21 (5%)	5/20 (25%)	<0·0001

Data are n/N (%), unless otherwise indicated.

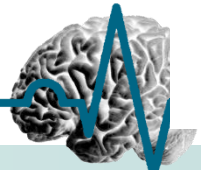


Table 3

Seizure frequency and risk by cure status

	Seizure events per day (n)		Seizure rates per year		Seizure rate ratios (95% CI)		
	Persistent infection	Resolved infection	Persistent infection	Resolved infection	Persistent infection	Resolved infection	p value
Overall period *							
All seizures	225	72	4.39	0.84	1.00	0.19 (0.15–0·25)	<0.0001
Partial	217	66	4.24	0.77	1.00	0.18 (0.14–0·24)	<0.0001
Generalised	9	6	018	0.07	1.00	0.40 (0.14–1.12)	0.081
Days 181–540‡							
All seizures	113	40	3.51	0.61	1.00	0.17 (0.12–0.25)	<0.0001
Partial	109	36	3.38	0.55	1.00	0.16 (0.11–0.24)	<0.0001
Generalised	4	4	012	0.06	1.00	0.49 (0.12–1.95)	0.311

In NCC: best way of sz control: terminate the ACTIVE infection

* 18 714 patients per days in non-cured periods and 31 273 patients per days in cured periods.

† 6960 patients per days in non-cured periods and 7200 patients per days in cured periods.

‡ 11 762 patients per days in non-cured periods and 24 073 patients per days in cured periods.

Am. J. Trop. Med. Hyg., 98(4), 2018, pp. 945–966
doi:10.4269/ajtmh.18-88751

Guidelines

Diagnosis and Treatment of Neurocysticercosis: 2017 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH)

A. Clinton White, Jr.,[1] Christina M. Coyle,[2] Vedantam Rajshekhar,[3] Gagandeep Singh,[4] W. Allen Hauser,[5] Aaron Mohanty,[6] Hector H. Garcia,[7,8] and Theodore E. Nash[9]

[1]*University of Texas Medical Branch, Galveston, Texas;* [2]*Albert Einstein College of Medicine, Bronx, New York;* [3]*Christian Medical College, Vellore, India;* [4]*Dayanand Medical College, Ludhiana, India;* [5]*Columbia University, New York, New York;* [6]*University of Texas Medical Branch, Galveston, Texas;* [7]*Instituto Nacional de Ciencias Neurologicas, Lima, Peru;* [8]*Universidad Peruana Cayetano Heredia, Lima, Peru;* [9]*National Institutes of Health, Bethesda, Maryland*

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We recommend albendazole (15 mg/kg/day) combined with praziquantel (50 mg/kg/day) for 10–14 days rather than albendazole monotherapy for patients with more than two viable parenchymal cysticerci (strong, moderate).

In NCC always add Corticosteroids

Acta Neuropathologica
https://doi.org/10.1007/s00401-018-1909-9

ORIGINAL PAPER

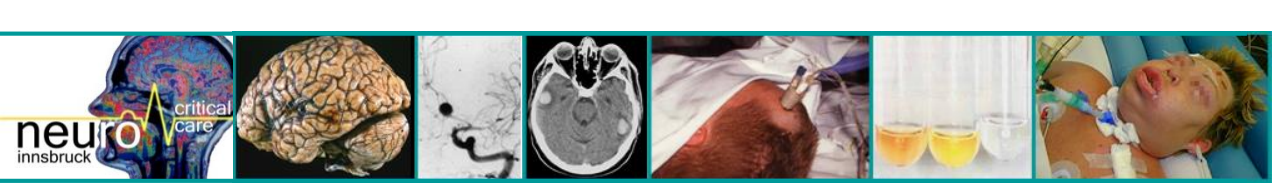
Nodding syndrome in Uganda is a tauopathy

Michael S. Pollanen[1,2] · Sylvester Onzivua[3] · Janice Robertson[4] · Paul M. McKeever[4] · Francis Olawa[5] · David L. Kitara[6] · Amanda Fong[2]

Received: 16 July 2018 / Revised: 11 September 2018 / Accepted: 11 September 2018

Abstract

Nodding syndrome is an epidemic neurologic disorder of unknown cause that affects children in the subsistence-farming communities of East Africa. We report the neuropathologic findings in five fatal cases (13–18 years of age at death) of nodding syndrome from the Acholi people in northern Uganda. Neuropathologic examination revealed tau-immunoreactive neuronal neurofibrillary tangles, pre-tangles, neuropil threads, and dot-like lesions involving the cerebral cortex, subcortical nuclei and brainstem. There was preferential involvement of the frontal and temporal lobes in a patchy distribution, mostly involving the crests of gyri and the superficial cortical lamina. The mesencephalopontine tegmental nuclei, substantia nigra, and locus coeruleus revealed globose neurofibrillary tangles and threads. We conclude that nodding syndrome is a tauopathy and may represent a newly recognized neurodegenerative disease.



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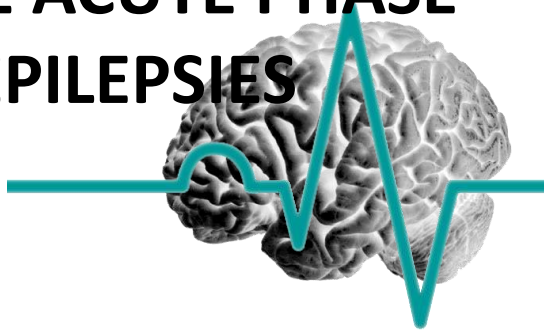


Chen *et al. Neuroimmunol Neuroinflammation* 2017;4:124-31
DOI: 10.20517/2347-8659.2017.17

Neuroimmunology and Neuroinflammation
www.nnjournal.net

Original Article Open Access

Analysis of clinical data of viral encephalitis patients complicated with epilepsy during the acute phase

in viral encephalitis:

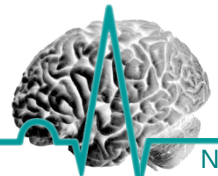
incidence of epileptic seizures :33.6%

mainly generalized seizures: 66.4%

encephalitic patients with sz: -more involvement of cortical regions in imaging
-higher level of glucose in CSF
-prognosis slightly poorer

Acute viral Meningoencephalitis

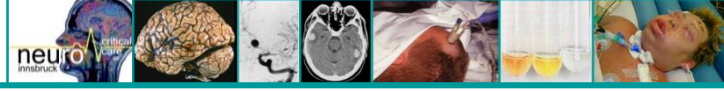
- after prodromal „signs and symptoms“ , incl fever
  - **headache**
  - **behavioural disturbance**
  - disorientation
  - confusion
  - hallucinations
  - somnolence/sopor/coma
  - **Focal or generalized epileptic seizures**
  - focal neurology
  - **Meningism (frequently only mild)**



Acute viral Meningoencephalitis

- after prodromal „signs and symptoms“ , incl fever
  - **headache**
  - **behavioural disturbance**
  - disorientation
  - confusion
  - hallucinations

  → **qualitative impairment of consciousness**
  - somnolence/sopor/coma → **quantitative**
  - **Focal or generalized epileptic seizures**
  - focal neurology
  - **Meningism (frequently only mild)**



Herpes simplex I Meningoencephalitis

Clinically indicative for Herpes simplex-Virus-1 Encephalitis (HSVE):

➔ Acyclovir i.v. and Neurocritical Care Unit

Herpes simplex I Meningoencephalitis

Signs and Symptoms

1. Flu like prodromal stage

2. **Focal** encephalitic stage:
   aphasia, mono- or hemiparesis,
   (pseudo-)psychotic symptoms
   seizures, focal, generalised
   impairment of consciousness

Most frequent Indications for **NICU admission**:

- **impairment of consciousness**
- epileptic seizures, **status epilepticus**
- **ventilation, airways**
- **impairment** of **swallowing**

Viral Meningoencephalitis

Neuro-/intensive care management:

- **Brain edema** (dexamethasone?, decompressve-craniectomy?)
- **Anticonvulsive Therapy in status epilepticus**
- **Analgesics and sedative drugs**

  CAVE: Neuroleptic drugs!
- optimal **temperature management**
- Therapeutic Hypotherma?
- **Multimodal Neuromonitoring**

Clinical Neurology and Neurosurgery 111 (2009) 399–406

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

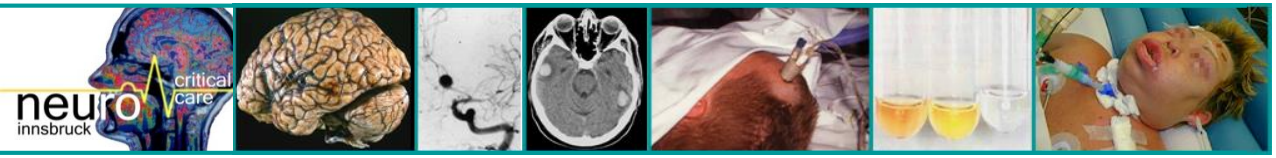
journal homepage: www.elsevier.com/locate/clineuro

Review

Raised intracranial pressure in acute viral encephalitis

Gyanendra Kumar[a,*], Jayantee Kalita[b], Usha Kant Misra[b]

[a] Department of Neurology, University of Missouri-Healthcare Columbia, Columbia, MO, USA
[b] Department of Neurology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP, India



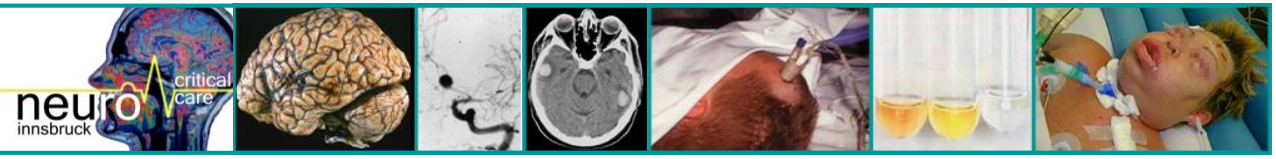
neurocritical care society Neurocrit Care (2016) 25:273–281
DOI 10.1007/s12028-016-0272-8

PRACTICAL PEARL

Neuroglucopenia and Metabolic Distress in Two Patients with Viral Meningoencephalitis: A Microdialysis Study

Mario Kofler[1] · Alois Schiefecker[1] · Ronny Beer[1] · Florian Sohm[2] · Gregor Broessner[1] · Paul Rhomberg[3] · Peter Lackner[1] · Bettina Pfausler[1] · Claudius Thomé[2] · Erich Schmutzhard[1] · Raimund Helbok[1]

2016 Oct; 25(2):273-81



International Journal of Infectious Diseases 51 (2016) 73–77

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

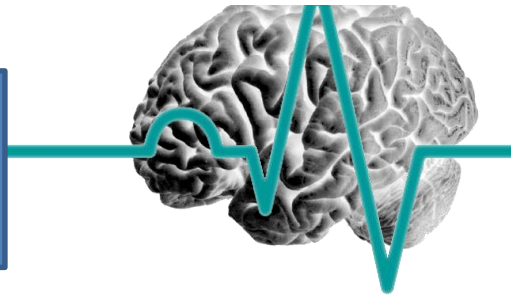
journal homepage: www.elsevier.com/locate/ijid

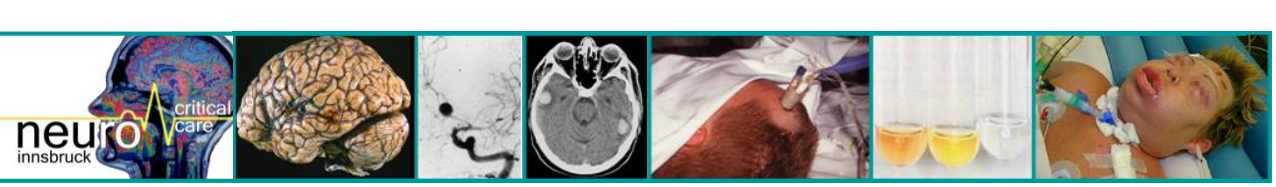
Short Communication

Cerebral glucose hypometabolism in Tick-Borne Encephalitis, a pilot study in 10 Patients

Anelia Dietmann [a,1,*], Daniel Putzer [b,c,1], Ronny Beer [a], Raimund Helbok [a], Bettina Pfausler [a], Abdul Jalil Nordin [d], Irene Virgolini [b], Astrid E. Grams [e], Erich Schmutzhard [a]

TBE: the older the more likely **encephalitic** course





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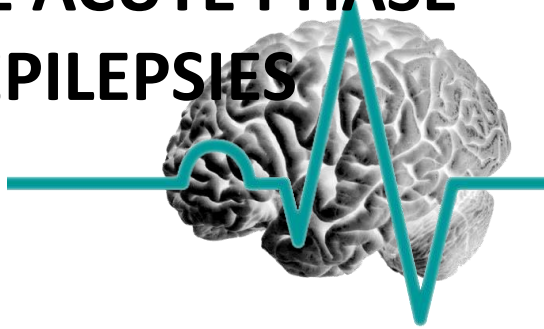

Epidemiology of brain abscess

incidence 0,4 – 1,3 /100.000 persons/year nowadays

decreasing incidence over decades

by improvement of the general health and medical access of the population *(-> data South Africa, USA)*

in childhood by early diagnosis and treatment of otitis, sinusitis *(Brasilia: 26% vs 11%)*

higher incidence in risk groups (-> immunosuppression)

male-to-female sex ratio of 2:1 to 3:1

median age of 30-40 years (meta-analysis of ~ 10 000 cases)

Goodkin, Saez-Llorenz, Brouwer, Sonneville

Focal infection of the brain - Abscess formation

highly susceptible to bacterial infections once the blood-brain barrier has been crossed- preexisting lesion necessary (necrosis, ischemia, hypoxia)

Early cerebritis (day 1 – 3)

perivascular inflammatory response
surrounding the necrotic center, no ring on CT

Late cerebritis (day 4 – 9)

central necrosis

Early capsule formation (day 10 – 13)

accumulation of fibroblasts and
neovascularization

Late capsule formation (beyond day 14)

host defenses act to wall off the abscess
well-formed capsule

Contiguous spread (per continuitatem)

responsible for 40-50% of brain abscess

focus

- middle ear, mastoid cells, paranasal sinuses
- cranial trauma (-> bone fragments, wound contamination)
- post neurosurgery
- (in close relationship to the primary infection)

typically located in frontal and temporal lobe

Etiology

Hematogenous dissemination

responsible for 30-40%

- **endocarditis** (13-23%, “multiorgan involvement”)
- pulmonary infections
- dental abscesses (↑*Laulajainen-Hongisto A et al, Infect Dis 2016*)
- osteomyelitis, intraabdominal infections, skin infections etc

tend to develop in the area supplied by the middle cerebral artery

Clinical signs and symptoms

Headache is the leading symptom (82% [64-97%])

focal clinical signs can be very subtle

classic triad of fever, headache, and focal neurologic deficits in <20%

Seizures: 25%

Symptoms and signs	
Headache	4,526/6,575 (69)
Nausea/vomiting	1,993/4,286 (47)
Fever	3,718/6,970 (53)
Altered consciousness	3,207/7,479 (43)
Neurologic deficits	2,996/6,241 (48)
Seizures	1,647/6,581 (25)
Nuchal rigidity	1,465/4,629 (32)
Papilloedema	845/2,428 (35)

Brouwer et al, Neurology 2014

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Brouwer et al, Neurology 2014

Diagnostic approach

CSF examination

NO routine CSF examination in brain abscess!

only in very selected cases with risk – benefit weighing

risk of cerebral herniation

risk of abscess rupture leading to ventricular empyema or pyocephalus

⟶ worsening of outcome!

normal CSF analysis does not exclude brain abscess

Diagnostic approach

CSF examination

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risk of cerebral herniation

risk of abscess rupture leading to ventricular empyema or pyocephalus

⟶ worsening of outcome!

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Blood examination

aerobic and anaerobic blood cultures prior to antimicrobial therapy (~30% pos)

Leucocyte count, and serum C reactive protein increased in ~60%

may be abnormal in most differential diagnosis

Treatment

- surgery (also for diagnosis)
- appropriate antibiotic therapy
- eradication of the primary source

Neurosurgery

stereotactic aspiration ≥ 1cm Ø by neuro - navigation

continuous drainage of abscess has to be considered

≥ 2,5cm Ø

periventricular location with high risk of intraventricular rupture

- **reduction of abscess size, decrease of ICP**
- **microbiological examination**

Antibiotic therapy

appropriate emipric antibiotic therapy depends on

-activity against the **suspected or proven** infecting flora (-> **focus**?)

-capacity to penetrate the brain tissue and intracranial pus

-good long-term safety profile (Cave: encephalopathy, seizures, ataxia)

-administrable both intravenously and orally

as soon as possible

starting after stereotactic aspiration depends on time of availability, patient‘s comorbidity, size and location of abscess

Underlying condition	Typical Pathognes
Otitis, mastoiditis, sinusitis	polymicrobial mainly streptococci, Enterobacteriaceae *Streptococcus pneumoniae* anaerobes (*Prevotella* sp., *Bacteroides* sp.), *S. aureus*
Cranial trauma	polymicrobial mainly *S.aureus*, *Streptococcus pyogenes* anaerobes (*Clostridium* sp., *Actinomyces* sp.)
Neurosurgery	polymicrobial mainly *S. aureus*, coagulase-negative staphylococci Enterobacteriaceae
Infective endocarditis	*Staphylococcus aureus* oral streptococci, HACEK bacteria
Dental infection	polymicrobial, mainly *Streptococcus milleri* group anaerobes (*Actinomyces* sp., *Prevotella* sp., *Bacteroides* sp., *Fusobacterium sp)*
Pulmonary circulation shunts (congenital heart disease	Polymicrobial, including streptococci anaerobes (*Actinomyces* sp., *Prevotella* sp., *Bacteroides* sp., *Fusobacterium* sp.)

focal spread

„streptococci“

„staphylococci“

„anaerobes“

hematogeneous spread

Clinical characteristics and outcome of brain abscess

Systematic review and meta-analysis

Matthijs C. Brouwer, MD, PhD
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ABSTRACT

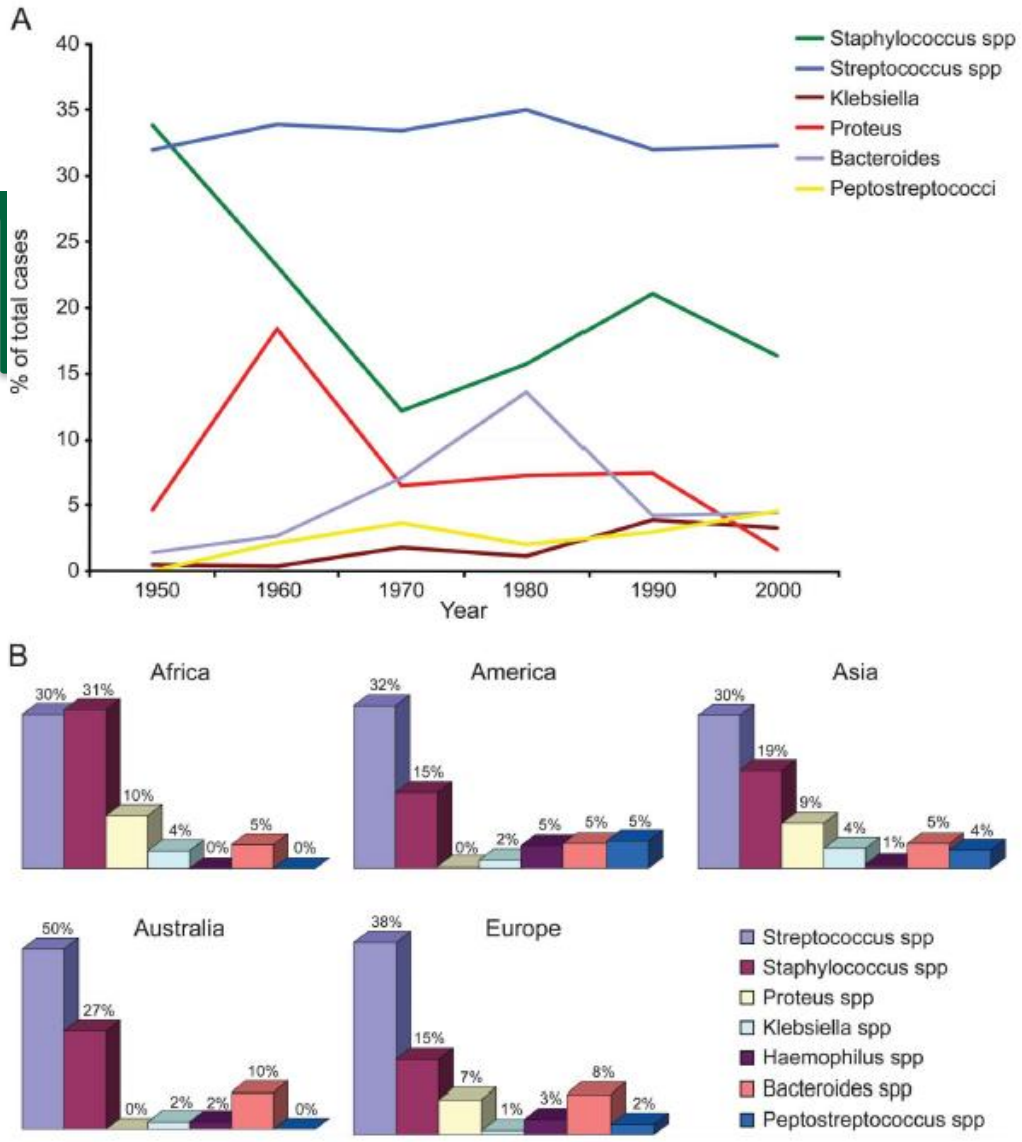
Objective: To define clinical characteristics, causative organisms, and outcome, and evaluate trends in epidemiology and outcome of brain abscesses over the past 60 years.

Methods: We performed a systematic review and meta-analysis of studies on brain abscesses published between 1970 and March 2013. Studies were included if they reported at least 10 patients with brain abscesses, included less than 50% extra-axial CNS infections (empyema) without brain abscess, and did not solely report on brain abscesses caused by a single pathogen.

Results: We identified 123 studies including 9,699 patients reported between 1935 and 2012. There was a male predominance of 2.4 to 1, and the mean age of patients with brain abscesses was 34 years. The most common causative microorganisms were *Streptococcus* and *Staphylococcus* species, comprising 2,000 (34%) and 1,076 (18%) of 5,894 cultured bacteria. Geographical distribution of causative microorganisms over continents was similar and did not substantially change over the past 60 years. Predisposing conditions were present in 8,134 of 9,484 patients (86%) and mostly consisted of contiguous or metastatic foci of infection. The classic triad of fever, headache, and focal neurologic deficits was present in 131 of 668 (20%) of patients. Case fatality rate decreased from 40% to 10% over the past 5 decades, while the rate of patients with full recovery increased from 33% to 70%.

Conclusions: The prognosis of patients with brain abscesses has gradually improved over the past 60 years. Important changes over time were the modality of cranial imaging, neurosurgical technique, and antimicrobial regimen. *Neurology*® 2014;82:806-813

Figure 1 Distribution of causative microorganisms through time and per continent



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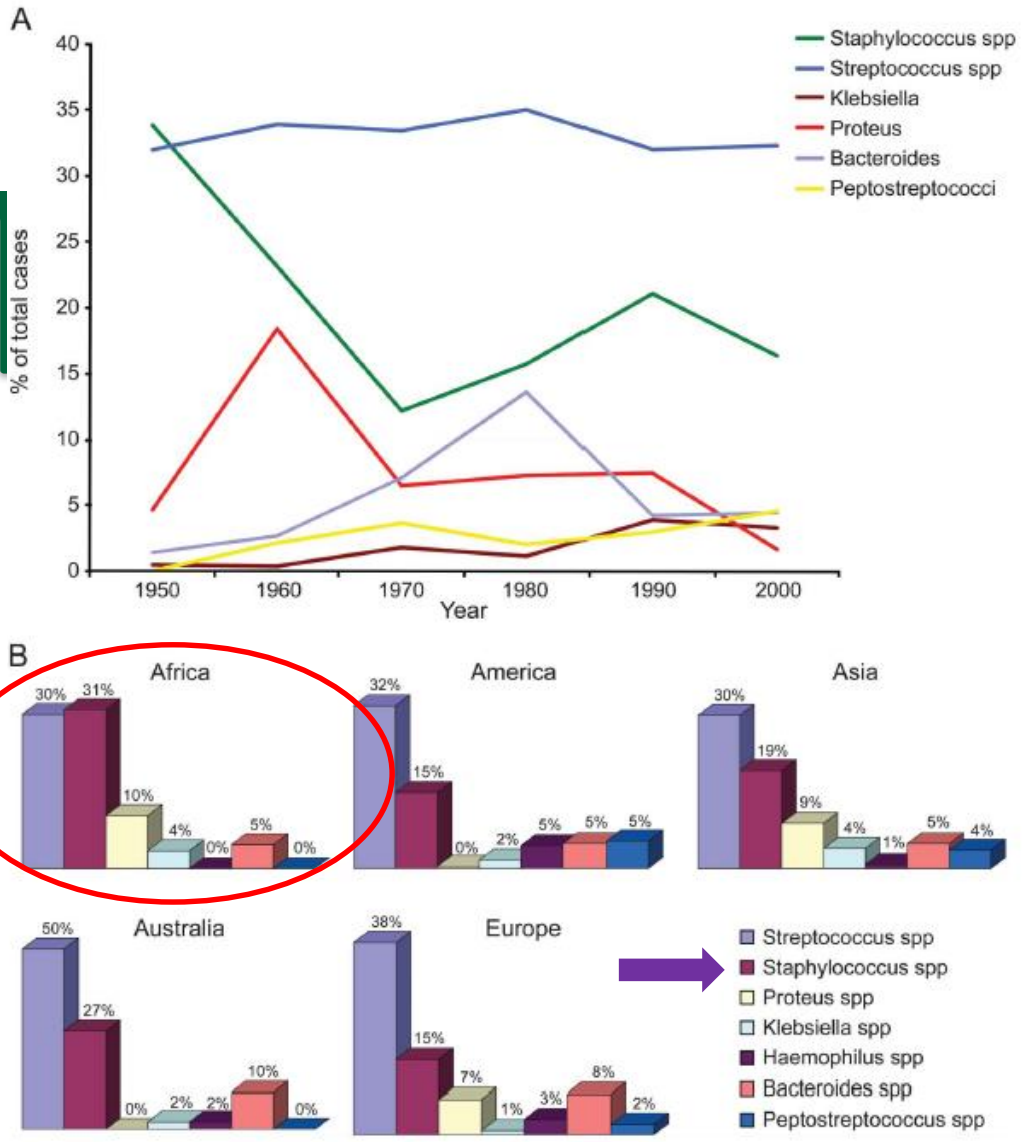


Cave:
MRSA

Empirical antimicrobial therapy in the immunocompetent

3rd or 4th cephalosporin*

+ metronidazole

+ oxacillin/ vancomycin/ linezolid/ rifampicin…

*alternatively meropenem

Empirical antimicrobial therapy in the immunocompromised

Bone marrow and solid organ recipients

Aspergillus spp., Candida spp., Nocardia, Toxoplasmosa gondii, atypical mycobacteria

3rd cephalosporin + metronidazole
+ trimethoprim–sulfamethoxazole or *sulfadiazine* (Nocardia spp)
+ voriconazole (Aspergillus)

AIDS patients

Toxoplasmosa gondii, Cryptococcus neoformans, Listeria monocytogenes, Mycobacterium spp., Aspergillus, Candida spp

*+ pyrimethamine plus sulfadiazine (*if antitoxoplasma IgG pos.)

Suspected M. tuberculosis

isoniazid, rifampin, pyrazinamide, ethambutol

CONTROVERSIES

Abscess irrigation **->** yes/no

Corticosteroids

only in patients with significant edema for max 5 days
decreased antibiotic penetration into the abscess

Continuing anaerobic therapy in case of negative microbiology

microbiological results might not identify all pathogens

neurotoxicity of metronidazole

Duration of therapy and when to switch from iv to po

at least 4-6 iv weeks duration according to therapy response
1-2 weeks iv and then po (Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy 2000)

Treatment

surgery
(also for diagnosis)

appropriate
antibiotic therapy

eradication of the
primary source

Complications and outcome

Improved over the last decades gradually

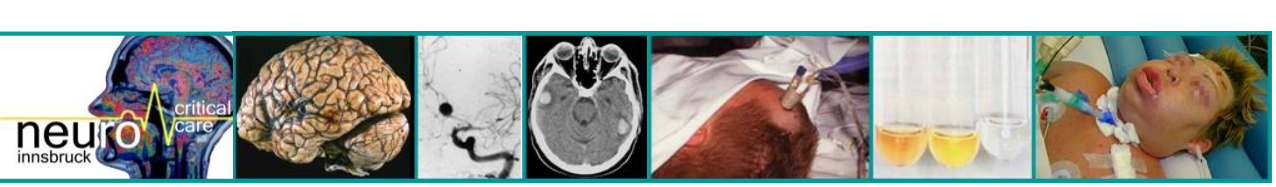
70% good outcome (minimal neurologic sequelae)

Mortality

declined from 40% in 1960 to 15% in the past decade

Hydrocephalus ± ventriculitis ± pyocephalus

mortality up to 85%



NEUROCYSTICERCOSIS AND OTHER HELMINTHIC DISEASES

ACUTE BACTERIAL MENINGITIS

BRAIN ABSCESS

ACUTE VIRAL ENCEPHALITIS

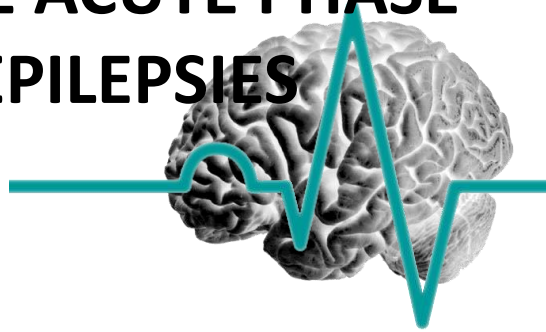
CHRONIC MENINGITIS INCL GRANULOMA (TB)

CEREBRAL MALARIA AND OTHER PROTOZOAL DISEASES

FREQUENT CAUSES OF

- SYMPTOMATIC EPILEPTIC SEIZURES IN THE ACUTE PHASE

- SYMPTOMATIC POSTENCEPHALITIC EPILEPSIES



Diagnosis **Cerebral Malaria**:

1) History (of exposure)

2) Impairment of consciousness, „severe prostration“, **epileptic seizures,** focal neurological signs and symptoms.

3) Positive blood smear

4) **Malaria retinopathy**

World Health Organization

Journal of Critical Care 28 (2013) 1086–1092

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Fosphenytoin for seizure prevention in childhood coma in Africa: A randomized clinical trial☆,☆☆,★★

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majority: cerebral malaria

no benefit

Journal of Critical Care 28 (2013) 1086–1092

Cochrane Library

Cochrane Database of Systematic Reviews

Routine anticonvulsants for treating cerebral malaria (Review)

Meremikwu MM, Marson AG

Main results

Three trials with a total of 573 participants met the inclusion criteria. These trials all compared phenobarbitone with placebo or no treatment. In the two trials with adequate allocation concealment, death was more common in the anticonvulsant group (Risk Ratio 2.0; 95% confidence interval 1.20 to 3.33; fixed effect model). In all three trials, phenobarbitone compared with placebo or no treatment was associated with fewer convulsions (Risk Ratio 0.30; 95% confidence interval 0.19 to 0.45; fixed effect model).

WILEY

Thank you