Nocardial Brain Abscess: Observation of Treatment Strategies and Outcome in Switzerland from 1992 to 1999

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Abstract

Background: Brain abscesses caused by *Nocardia* spp. are rare, but life-threatening infections that are notoriously difficult to diagnose and treat and which occur mainly in immunocompromised patients. Standard treatment guidelines are not available.

Methods: A systematic search for nocardial brain abscesses from 1992 to 1999 was conducted in Switzerland for the comparison of clinical presentation, treatment strategies and outcome.

Results: Seven cases were found, for which data of six were available. In 4/6 patients antimicrobial therapy led to a decrease in the size of abscesses. Four of six patients died. The cause of death was likely due to underlying co-morbidities, rather than the nocardial infection.

Conclusion: The finding that treatment was different in each case underscores the lack of therapeutic guidelines.

Key Words

Nocardia · Brain abscess · Therapy · Antibiotics · Switzerland

Infection 2001; 29: 337–341
DOI 10.1007/s15010-001-1147-1

Introduction

Nocardia spp. are aerobic, branching, partially acid-fast actinomycetes that inhabit the soil. Infection with *Nocardia* spp. is favored by immunosuppression, but it can also occur in otherwise healthy subjects. The organism enters the body via inhalation or direct percutaneous inoculation. Nocardial infection remains localized or disseminates, most often hematogenously from a primary lung focus. In larger microbiological, clinical and autopsy reviews 10–45% of patients with nocardiosis had CNS involvement [1–5].

Nocardial brain abscesses can be life-threatening and pose diagnostic and therapeutic problems to the microbiologist and the clinician. Since the first description in 1890, virtually all reported cases died until 1954, when a patient was successfully treated with a combination of surgery and antibiotic therapy [6–8]. Since the advent of computed tomography as a diagnostic tool, mortality dropped significantly for immunocompetent patients (20%), whereas it remains unacceptably high for immunocompromised patients (55%) [9]. Multiple abscesses have a higher mortality rate than solitary ones, abscesses due to *Nocardia farcinica* have a higher mortality rate than those caused by *Nocardia asteroides* [3, 9].

Given the lack of evidence-based therapeutic guidelines, we conducted a systematic search for nocardial brain abscesses in Switzerland from 1992 to 1999, to compare recent treatment strategies and outcome.

Methods

A letter was sent to the Institutes of Microbiology in Basel, Bern, Geneva, Lausanne, Lugano, Sion, St. Gallen and Zurich, asking them to review their databases from 1992 to 1999 for *Nocardia* isolates from cerebral abscesses. A similar letter was sent to infectious disease specialists in all hospitals where the specialty is represented and to the heads of all internal medicine clinics with more than 60 beds, asking if they had knowledge of patients with nocardial brain abscesses from 1992 to 1999. With the help of these colleagues we were able to identify seven cases with one each from Aarau, Geneva, Lausanne, Lugano and Schaffhausen/Zurich and two from Bern. Furthermore, we asked for a copy of the letter of discharge of these patients and the results of the susceptibility testing if it had been done. Two practitioners were contacted to inquire about patients' present health.

Results

We obtained the requested data for all but one patient. In the following section a comparison of the available clinical data for the six patients is presented. The data are summarized in table 1. The median age at diagnosis was 60 years (range 44–73 years). The male to female ratio was 2 : 1. All but one had serious underlying diseases and all received corticosteroid treatment for more than 1 month. The me-

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Received: Sepember 12, 2000 • Revision accepted: September 13, 2001

Table 1
Clinical characteristics, treatment time course and outcome of Swiss patients from 1992 to 1999.

Patient no.	**1**	**2**	**3**	**4**	**5**	**6**
Year	1993	1994	1994	1998	1999	1999
Age/sex	51/M	61/M	61/F	59/M	73/M	44/F
Co-morbidities (therapeutic interventions)	Kidney transplant (prednisone, azathioprine, cyclosporin)	Sarcoidosis (prednisone) diabetes heart failure	Sarcoidosis (prednisone) heart failure	Glioblastoma (dexamethasone, operated 1 year earlier, radiotherapy)	ITP[a] (prednisone) splenectomy myelodysplasia diabetes heart failure	Suspected asthma (prednisone)
Abscess localization in the brain (size)	Parieto-occipital bilateral, multiple (<1cm)	Parietal	Cerebellum	Occipital, tumor excision site	Frontal (2.5cm)	Fronto-basal (1.3cm)
Other localization	Lung soft tissue	-	-	Soft tissue (adjacent)	Soft tissue	Lung soft tissue
Fever	Yes	No	No	Yes	Yes	Yes
Neurological symptoms	Dysmetria, facial weakness	Vertigo, hemiparesis, falls, seizure	Headache	Aphasia, hemiparesis, draining abscess	Headache, dizziness, falls, nuchal rigidity	None
Onset of disease related symptoms	Day - 20	Day - 14	Day - 30	Day - 10	Day - 35	Day - 255
Diagnostic suspicion	Day - 1	Day - 2	Day - 1	Day - 1	Day - 1	Day - 1
Start of antibiotic treatment	Day - 1 Minocyclin/ imipenem	Day - 2 Ceftriaxone/ amikacin	Day - 1 Co-trimoxazole	Day - 1 Ceftriaxone/ rifamipicin day + 5: + amikacin	Day - 9 Ceftriaxone/ amoxicillin (suspicion of meningitis)	Day - 0 Ceftriaxone/ amikacin
Start co-trimoxazole	Day + 7	Day +2	Day - 1	-	Day + 1	Day + 42 (outpatient only)
Antibiogram available	Day + 33	-	Day + 112	Day + 16	Day + 23	Day + 22
Day of discharge	-	Day + 28	Day + 10	-	-	Day + 42
Day of death Reported cause	Day + 80 Ruptured aortic aneurysm	Day + 224 Coronary heart disease	-	Day + 8 Sepsis	Day + 35 Valvular heart disease	-
End of outpatient treatment	-	Day + 224	Day + 365	-	-	Day + 165
Duration of follow-up	-	-	> 6 years	-	-	> 1 year
Surgery	None	Stereotactic	Craniotomy	Craniotomy ventricular drainage	Aspiration ventricular drainage	None
Abscess regression observed	Yes	Yes	Yes	No	No	Yes

Day 0 is defined as the time point when diagnosis was highly probable based on a positive result in microscopic examination of biopsy samples;
[a] ITP: idiopathic thrombocytopenic purpura

dian time from the start of symptoms related to the nocardial disease to the suspicion of the diagnosis was 25 days and ranged from 10 days to more than 7 months. The longest interval was found for the least immunocompromised patient who presented repeated episodes of fever and cough and later painful soft tissue abscesses, but no symptoms of brain involvement. Four of six patients had fever. Patients 1, 5 and 6 first received other antibiotics for suspected pulmonary infection.

Abscesses were localized throughout the brain, in one case in the cerebellum, in one case in a tumor excision bed. One patient had multiple small abscesses. Two patients had abscesses exclusively in the brain, whereas the others also had subcutaneous, muscular, bone or pulmonary abscesses. The two patients with only brain localization did not have fever.

Four of six patients underwent neurosurgery, with varying types of intervention (craniotomy and excision, stereotactic or standard aspiration, in two cases additional ventricular drainage). The two conservatively treated patients had relatively small sized abscesses (1–1.3 cm).

Antibiotic treatment was different in each case. The combination of ceftriaxone and amikacin was chosen in three cases, in one case together with rifampicin. In one case it was again stopped because of insufficient back-up from the literature, and co-trimoxazole was introduced. Co-trimoxazole was therefore the main component of inpatient treatment in four patients. No adverse reactions were described. One patient received intrathecal amikacin and one received co-trimoxazole prophylaxis after successful cure. Susceptibility testing was done in all but one patient (Table 2). Since 1999 the results were reported as MIC. Immunosuppressive therapy was tapered only in patient 1 (kidney transplant) and already stopped in patient 6 (suspicion of asthma). Abscesses regressed in four patients who lived long enough for radiological follow-up. Three patients died while still in hospital due to an unrelated cause. Three patients were discharged on a treatment based on co-trimoxazole, one of them died approximately 8 months later due to an unrelated disease, the two others are still alive and well after 14 months and 6 years, respectively. Both survivors were women.

Discussion

Seven brain abscesses due to *Nocardia* spp. in 7 years, or one patient per year is in the range that we expected for Switzerland based on extrapolation of data from studies in France and Italy [3, 4]. We therefore believe that data from the larger microbiological laboratories were thoroughly reviewed and that we did not miss more than one case. The male to female ratio of 2 : 1 corresponds to other published data [9].

The treatment strategies for the presented patients, as different as they were, were justified by the individual case presentation and based on reflections from the literature. The small number of cases and the poor overall outcome does not enable the most effective regimen to be determined.

Antibiotic Therapy

The choice of antibiotics for the treatment of CNS infections is not only based on susceptibility, but also on CSF penetration of the drug at nontoxic doses. Susceptibility testing in *Nocardia* spp. is encumbered by the lack of standardized methods and the difficulty in growing the organisms uniformly. E-tests are now commonly done and results given as MIC, although radiometric methods may be more accurate

Table 2
Species identification and susceptibility testing results (selection).

Patient no.	**1**	**2**	**3**	**4**	**5**	**6**
Species	*N.asteroides*	*N.asteroides*	*N.farcinica*	*N.farcinica*	*N.farcinica*	*N.asteroides*
Susceptibility testing method	Disk diffusion	Not done	Disk diffusion	Disk diffusion	E-test	E-test
Amoxicillin/clav.acid	R		S	S	4 mg/l	
Cefuroxime	R		S			0.75 mg/l
Ceftriaxone	S		S	S	>256 mg/l	0.5 mg/l
Imipenem	S		S	S		32 mg/l
Meropenem					32 mg/l	32 mg/l
Amikacin	S		S	S	1.5 mg/l	0.25 mg/l
Gentamicin	S		R	R		
Tobramycin	S		R	R		
Ofloxacin				R		
Norfloxacin			I			
Ciprofloxacin	S		S		1.5 mg/l	
Trovafloxacin					8 mg/l	
Co-trimoxazole	S		S		2.5 mg/l	0.064 mg/l

S: sensitive;
I: intermediate;
R: resistant

[10–12]. In the past, poor correlation between antibiotic susceptibility *in vitro* and their efficacy in experimental models was reported [13].

Sulfonamides and trimethoprim/sulfamethoxazole (co-trimoxazole) have been in clinical use for half a century and are considered standard antimicrobial agents for the therapy of patients with nocardial infections. Co-trimoxazole is still favored by the most cited therapeutic recommendations [9]. The two components show *in vitro* synergy in many but not all strains, and a higher than usual trimethoprim to sulfamethoxazole ratio may be necessary for optimal treatment [14, 15]. In addition, co-trimoxazole achieves good CSF drug levels [9, 16].

While the rates of isolates susceptible to co-trimoxazole *in vitro* are high, a study on 63 clinical isolates found susceptibility rates of 7.5% and 0% for *N. asteroides* and *N. farcinica*, respectively [3]. Methodological aspects and geographical variation might have contributed to this discrepancy.

The published recommendations for the treatment of nocardial brain abscesses using co-trimoxazole rely on small series of patients from the seventies or eighties containing no or single brain abscesses with survival rates for the latter of only 50-60% [14, 17, 18]. Many clinical failures are described [15, 19]. Adverse reactions (common in patients with AIDS), myelotoxicity, nephrotoxicity and drug interactions with cyclosporin must be considered [20]. Interestingly, co-trimoxazole failed to change the disease fatality before the introduction of neurosurgery [8].

Possible alternatives include amikacin-containing regimes, as there are virtually no *Nocardia* isolates resistant to amikacin *in vitro* [3, 4]. Amikacin has shown *in vitro* synergism in combination with co-trimoxazole and additive effect in combination with imipenem and cefotaxime [21, 22]. The successful clinical combination of amikacin with ceftriaxone, cefuroxime and co-amoxiclav has been described in case reports [22–25], sometimes as a triple combination with co-trimoxazole [24, 25]. The combination of amikacin and imipenem may be a good choice for an initial blind treatment, since all, even the notoriously resistant *N. farcinica*, are susceptible to these two drugs and successful treatment with this regimen has been reported [3, 4, 8].

Imipenem also showed *in vitro* synergism with co-trimoxazole [21]. Fluoroquinolones have revealed poor activity *in vitro* at achievable serum and CSF drug levels, which makes them rather inappropriate for nocardial brain infections [26, 27].

Neurosurgery

Recent reviews and case reports refer to a retrospective analysis by *Mamelak* et al. [9] for treatment guidelines. These differ slightly from guidelines for the treatment of other brain abscesses. If *Nocardia* spp. have been isolated form an extraneural site and the cerebral lesion is < 2 cm, antibiotic treatment alone is recommended. In case of deterioration or nonresponse after 4 weeks, the lesion should be stereotactically aspirated for decompression and diagnostic confirmation. All abscesses larger than 2.5 cm should be primarily aspirated and craniotomy should be performed in case of deterioration or nonresponse. Repeated aspiration is reserved for surgically inaccessible lesions. Again, these guidelines are based on a small series of patients treated by *Mamelak* et al. [9], combined with an extensive, but potentially biased review of 131 reported cases.

Prophylaxis

Prophylaxis with co-trimoxazole does not reliably protect against nocardial infections [28, 29] and no data on relapse prevention are available.

Immunosuppression and Underlying Disease

An important observation in our compilation of cases is that most patients died of their underlying disease or of new complications due to their immunosuppression. Patient 4 who died after 1 week, had a glioblastoma with a very short survival prognosis; patient 5 who died after 7 weeks, had multiple co-morbidities. The two surviving patients are probably the ones with the least important co-morbidities. It is not known whether the discontinuation of immunosuppression changes the outcome of the disease.

In summary, when confronted with the diagnosis of a nocardial brain abscess, Swiss clinicians tend to favor treatment with co-trimoxazole. In the absence of prospective studies for this rare disease, convincing evidence for newer combinations will have to be collected with the help of case reports or observational studies.

Acknowledgments

We would like to thank all the participating physicians and microbiologists. Without their help this review would not have been possible.

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