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**BRAIN ABSCESS ASSOCIATED WITH
AGGREGATIBACTER
ACTINOMYCETEMCOMITANS: CASE REPORT
AND REVIEW OF LITERATURE**

Janette Rahamat-Langendoen, Marit van Vonderen, Lex Engström, Willem
Manson, Arie Jan van Winkelhoff, Esther Mooi-Kokenberg

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BRAIN ABSCESS ASSOCIATED WITH AGGREGATIBACTER ACTINOMYCETEMCOMITANS: CASE REPORT AND REVIEW OF LITERATURE



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2 BRAIN ABSCESS ASSOCIATED WITH AGGREGATIBACTER
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4 ACTINOMYCETEMCOMITANS: CASE REPORT AND REVIEW OF LITERATURE

Deleted: Arie Jan van Winkelhoff^{†,‡}

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Short running title:

Poor dentition risk for severe infection

Keywords: *Aggregatibacter actinomycetemcomitans*, periodontal disease, brain abscess, extra oral infection, sequence analysis

For Peer Review

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1
2 Abstract

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4 Introduction

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6 *Aggregatibacter actinomycetemcomitans* is considered a major pathogen in localized and
7
8 generalized aggressive periodontitis. *A. actinomycetemcomitans* has been found in various extra
9
10 oral infections and most frequently in endocarditis. We report a patient with multiple brain
11
12 abscesses due to infection with *A. actinomycetemcomitans* and review the English language
13
14 literature related to this subject.

15
16 Case report

17
18 A 42-year old patient with no underlying medical conditions presented with multiple brain
19
20 lesions initially thought to be metastatic lesions of a tumor of unknown origin. Findings during
21
22 drainage and subsequent histopathological conclusions made infection more likely. Culture of
23
24 drained material remained negative; however 16S rDNA PCR and sequence analysis on direct
25
26 material revealed *A. actinomycetemcomitans* as the causative agent of the infection. The most
27
28 likely source of infection was the poor dentition of the patient. After repeated drainage of the
29
30 lesions and antibiotic treatment the patient gradually improved, although cognitive impairment
31
32 remained.

33
34 Conclusions

35
36 Our report illustrates that a poor dental condition, notably destructive periodontal disease, can be
37
38 a risk for life threatening extra oral disease, and thus contributes to the total inflammatory burden
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40 of the body.

Deleted: intracranial abscess formation.
We have also shown that in cases of
culture-negative results, molecular
detection and identification can be an
essential adjunctive tool.

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Clinical relevance

Scientific rationale for study

Aggregatibacter actinomycetemcomitans is a major pathogen in periodontitis. In this case report we show the relevancy of oral health in relation to life threatening extra oral infection.

Principal findings

A 42-year old patient with poor dentition was found to have multiple brain abscesses caused by *Aggregatibacter actinomycetemcomitans*, detected by 16S rDNA PCR and sequence analysis on direct material.

Practical implications

Poor oral health is an important contributing factor to severe extra oral infection. We illustrate the diagnostic value of gene amplification and sequencing from direct specimens for patients with culture negative infections.

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2 Introduction

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4 Dental condition has been linked to several non-oral diseases such as infectious bowel diseases,
5
6 atherosclerosis, coronary heart diseases, stroke, diabetes and rheumatoid arthritis. The link
7
8 between destructive periodontal disease and these chronic disorders can be explained by common
9
10 risk factors such as smoking, stress and possibly genetic traits.

11
12 Periodontitis is a bacterial infection of the tooth-supporting tissues characterized by a large
13
14 inflamed and necrotic area associated with a high bacterial load and destruction of the alveolar
15
16 bone.(Nesse et al 2008) The infected periodontium can act as a focus for extra oral infections by
17
18 dissemination of periodontal bacteria to non-oral body sites. Periodontitis may thus contribute to
19
20 the total inflammatory burden of the body.

21
22 *Aggregatibacter actinomycetemcomitans* is considered a major pathogen in localized and
23
24 generalized aggressive periodontitis.(Zambon 1985) *A. actinomycetemcomitans* has been found
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26 in various extra oral infections, most frequently in endocarditis.(van Winkelhoff & Slots 1999)
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28 We report a patient with multiple brain abscesses due to infection with *A. actinomycetemcomitans*
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30 and review the English language literature related to this subject.
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2 Case report

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4 A 42-year old man was admitted to the Medical Centre Leeuwarden with a 3 days history of
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6 confusion and reduced consciousness. Besides heavy smoking and alcohol abuse there was no
7
8 relevant medical history. Physical examination revealed a slowly reacting man, who did not
9
10 respond adequately. Oral examination showed severe candidiasis and the orthopantogram
11
12 revealed caries profunda in multiple teeth and severe periodontal breakdown. (Figure 1)
13
14 There was no heart murmur and petechiae were not seen. No focal signs were detected at
15
16 neurological examination. Laboratory data revealed an elevated white blood count ($17.1 \times 10^9/L$)
17
18 and a moderately elevated C-reactive protein (34 mg/L). Liver enzymes and renal function tests
19
20 showed normal values. Computed Tomography (CT) of the brain showed multiple intracerebral
21
22 lesions with, after injection of intravenous contrast, ring enhancement surrounded by oedema.
23
24 (Figure 2) The lesions were primarily thought to be brain metastases of an unidentified tumour.
25
26 Magnetic Resonance Imaging (MRI) confirmed the findings with no signs of lesions elsewhere in
27
28 the body. A chest X-ray provided no indications for malignancy in the lungs. Serological tests for
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30 infection with HIV and Toxoplasma were negative. Blood cultures taken at admission were
31
32 negative. The patient was treated with dexamethasone. A follow-up CT after 4 days showed no
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34 improvement regarding the cerebral lesions and the surrounding oedema. The patient was
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36 transferred to the University Medical Centre Groningen for stereotactic biopsy and further
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38 treatment. Upon biopsying the lesions appeared to be abscesses and pus was collected from a
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40 lesion in the right frontal region. Histopathological examination revealed reactive inflammatory
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42 changes with necrosis and no signs of malignancy. At gram staining no microorganisms and few
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44 leucocytes were seen. Blood, chocolate, and MacConkey's 3 agar and Fastidious Broth were
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46 inoculated and incubated in air with 5% CO₂ at 35°C. Anaerobic cultures were performed on
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48 selective media and incubated in 80% N₂, 10% H₂, and 10% CO₂. The plates were examined for
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50 the presence of colonies over the course of 10 days. Post-operative empiric intravenous antibiotic

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2 treatment was initiated with ceftriaxone 2 gram bid, metronidazole 500 milligram bid and
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4 penicillin 6 times a day 2 million units. Aerobic and anaerobic culture remained negative and 16S
5
6 rDNA PCR and sequence analysis on direct material was performed four days after drainage.
7
8 Sequence data were compared with known sequences of 16S rDNA in the National Centre for
9
10 Biotechnology Information Genbank. The highest similarity (99.8%) was found with *A.*
11
12 *actinomycetemcomitans*. No other micro-organisms were detected. The patient continued to
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14 receive ceftriaxone and metronidazole intravenously, because a mixed anaerobic infection could
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16 not be excluded definitively. During his stay at the hospital the patient did not develop signs of
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18 endocarditis. A trans-thoracic echocardiogram made one week after operation showed no valvular
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20 vegetations. Besides his poor oral health no other focus of infection could be found. Nine days
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22 after the operation the patient deteriorated with reduced consciousness. CT of the brain showed
23
24 no signs of expansion of the lesions, but because of the deterioration it was decided to drain four
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26 lesions. During this operation the oral surgeon extracted five teeth because of advanced
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28 periodontal breakdown. Although the patient gradually improved, supported by diminishment of
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30 the lesions on CT scan, cognitive impairment remained. In the convalescent period the patient
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32 developed focal epilepsy with secondary generalisation. Treatment with sodium valproate was
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34 started. Parenteral antibiotic treatment was continued for 6 weeks, after which the patient was
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36 transferred to a rehabilitation centre for intensive rehabilitation. His condition improved rapidly
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38 and after four weeks he was able to return to his home. Besides epileptic seizures which made
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40 four short term admissions to the hospital necessary during a one year follow up, he showed no
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42 other sequelae of his disease.▼

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Discussion

A. actinomycetemcomitans is a non motile, facultative anaerobic small gram negative coccobacillus.(von Graevenitz & Zbinden 2007) Its fastidious slow growing nature makes it difficult to isolate through culture, especially because it is often part of mixed infection with other bacteria. Incubation on blood and chocolate agar for at least 48 hours is needed in enhanced atmosphere with CO₂. *A. actinomycetemcomitans* was first described as a human pathogen in 1912 by Klinger.(Klinger 1912) It was initially isolated in conjunction with *Actinomyces israelii*, leading to the speculation that *A. actinomycetemcomitans* itself was not capable of causing disease. After the introduction of penicillin, which eradicated *Actinomyces*, pure cultures of *A. actinomycetemcomitans* were increasingly reported from various body sites and organs.(Page & King 1966) It is recognized as one of the major pathogens in periodontitis. Besides, it is reported as cause of soft tissue infection (usually in association with *A. israelii* or *A. meyeri*) and endocarditis. Rarely, *A. actinomycetemcomitans* has been isolated from patients with endophthalmitis, septic arthritis, osteomyelitis, pneumonia, empyema, infected pacemaker wire and spinal epidural abscess. (Kaplan et al 1989;Yuan et al 1992;van Winkelhoff et al 1993;Binder et al 2003) Extra oral infections are thought to occur due to hematogenous dissemination from the infected periodontium.(van Winkelhoff & Slots 1999) Indeed, the poor dentition of our patient is thought to be the most likely source of infection, although we have no information regarding the presence or absence of *A. actinomycetemcomitans* in material of the extracted teeth. Also, the oral candidiasis may have been a factor that has facilitated invasion of *A. actinomycetemcomitans*. Endocarditis was considered unlikely because of the absence of clinical signs of endocarditis and the absence of vegetations at echocardiography.

A review of the English language literature reveals 12 reports of brain abscesses due to infection with *A. actinomycetemcomitans*.(Martin et al 1967;Burgher et al 1973;Brewer et al 1975;Ingham et al 1978;Garner 1979;Churton & Greer 1980;Kaplan, Weber, Oddone, & Perfect 1989;Zijlstra

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1
2 et al 1992;Kuijper et al 1992;Renton et al 1996;Stepanovic et al 2005) (Table 1) All but two
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4 reports are of male patients in the age of 19 to 62 years. In 6 patients the most probable source of
5
6 infection was poor dentition or recent dental therapy, emphasizing the importance of considering
7
8 the dental region as the origin of brain abscesses due to *A. actinomycetemcomitans*. Also, in 6
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10 patients the insidious onset of symptoms was more characteristic of a neoplastic rather than an
11
12 infectious process, as was the initial suspicion in our patient. Culture of the brain lesions revealed
13
14 mixed infection with associated aerobic and anaerobic micro-organisms in six patients; not
15
16 surprisingly, considering the source of infection, the identified micro-organisms were mainly
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18 common pathogens of the oro-pharyngeal region.

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20 The optimal treatment of brain abscesses consists of surgical drainage combined with antibiotic
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22 therapy. *A. actinomycetemcomitans* is usually susceptible to cephalosporins (especially third
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24 generation cephalosporins), ampicillin, rifampin, fluoroquinolones, trimethoprim-
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26 sulfamethoxazole, aminoglycosides and chloramphenicol. In vitro, there is variable susceptibility
27
28 to penicillin. Clindamycin and metronidazole have poor activity against *A.*
29
30 *actinomycetemcomitans*, but metronidazole in combination with amoxicilline has shown strong
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32 synergistic effect.(Steinberg & Burd 2009)

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34 The multiplicity of antibiotic regimes that has been used and the small number of patients do not
35
36 permit identification of the ideal therapeutic regimen. Because of the potential of beta-lactamase
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38 production and the difficulties with susceptibility testing because of fastidious growth, third
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40 generation cephalosporins are now considered the drugs of choice. The empirical treatment of our
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42 patient consisted of ceftriaxone, metronidazole and penicillin, accounting for the micro-
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44 organisms to be suspected in a brain abscess (streptococci, gram negative aerobes, and strict
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46 anaerobes). Based on the outcome of 16S rDNA PCR and sequence analysis, in combination with
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48 the most likely periodontal source of infection, it was decided to continue therapy for 6 weeks
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50 with ceftriaxone and metronidazole intravenously. To achieve definite improvement however a

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2 second surgical drainage was necessary, which emphasizes the importance of surgical treatment
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4 of brain abscesses.
5
6 Our report also illustrates the diagnostic value of gene amplification and sequencing from direct
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8 specimens for patients with culture negative infections who have a high likelihood of a bacterial
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10 infection. Microbiological detection of organisms in brain abscesses primarily relies on
11
12 microscopic examination and culturing of abscess pus specimen collected during neurosurgical
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14 drainage. However, the incidence of negative cultures can be high, especially in patients in whom
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16 antibiotic therapy started before collection of the specimen.(Tseng & Tseng 2006) Indeed, despite
17
18 meticulous handling of the specimen and prolonged incubation in aerobic as well as anaerobic
19
20 conditions, the cultures from our patient remained negative. Molecular detection of micro-
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22 organisms in direct material can be used to overcome the limitations of culture-based bacteria
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24 detection.(Tsai et al 2004;Al Masalma et al 2009) Although susceptibility testing is not feasible
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26 for culture negative, PCR positive specimens, molecular identification can guide the choice of
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28 antimicrobial treatment, thereby shortening the period of empirical treatment with multiple broad
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30 spectrum antibiotics.
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1
2 Conclusion

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4 We describe a patient with multiple culture negative brain abscesses initially thought to be brain
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6 metastases of an unidentified tumour. Detection and identification of the oral pathogen *A.*
7
8 *actinomycetemcomitans* was established by 16S rDNA sequencing on direct material, giving
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10 guidance to diagnosis and therapy. The patient's well documented destructive periodontal disease
11
12 is considered the most likely focus of infection. Also, the oral cavity has been identified as the
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14 primary ecological niche of *A. actinomycetemcomitans*. This report illustrates that severe
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16 periodontal infection can be a risk for serious and life threatening extra oral disease.

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Deleted: We have shown that poor oral health can be a risk factor for life threatening intracranial infection by a periodontal pathogen.

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1
2 Tables and figure legends

3
4 Figure 1

5
6 Orthopantomogram revealing caries profunda in multiple teeth and severe periodontal breakdown

7
8 Figure 2

9
10 Computed Tomogram brain. Abscesses visible in right and left cerebrum.

11
12
13 Table 1. Reported cases of cerebral abscesses due to infection with *A. actinomycetemcomitans*.

14
15 Pen = penicillin

16 Chlo = chloramphenicol

17 Co = colistin

18 Amp = ampicillin

19 Strep = streptomycin

20 Ge = gentamycin

21 Me = metronidazole

22 Amox = amoxicillin

23 Cefo = cefotaxime

24
25 Wk = week

26 Mo = month

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28 M = male

29 F = female

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sex/age (yr)	underlying illness	source	presenting symptoms	localisation	infection	mixed with	antibiotic treatment	duration	outcome	author/year
M/62	Carcinoma left ear	Otogenous	Drainage left ear, confusion	Posterior inferior temporal region	Single		Pen + Chlo + Co	3 wks (until death)	Died	Martin B.F., 1967
M/31	None	?	Right hemianopsia	Left parietal-occipital	Single		Amp + strep	2 wks	Recovered	Burgher L.W., 1973
?	?	?			Single		?	?	?	Brewer, 1975
?	?	?				?	?	?	?	Brewer, 1975
M/34	None	Dental	Headache, vomiting	Left frontal region		Anaerobic streptococci, Fusobacterium polymorphum, Bacteroides melaninogenicus, S. milleri	Amp + Ge + Me	?	Recovered	Ingham H.R., 1978
F/7	Cyanotic congenital heart disease	?	Headache, irritability	Left frontal region	Single		Clo	At least 4 wks	Recovered	Garner J.G., 1979
M/36	None	Dental	Headache, convulsion	Right frontal lobe		Fusobacterium nucleatum	Me + Chlo	?	Recovered	Churton M.C., 1980
F/15	Neurosurgery for meningioma	Nasopharynx	Headache, fever	Right frontal region		Eikenella corrodens, H. aphrophilus	Chlo + Me	1 mo	Recovered	Kaplan A.H., 1989
M/44	Alcohol abuse, emphysema	Dental	Right sided weakness, speaking disorder	Left fronto-parietal region, right occipital		Actinomyces meyeri	Amox	12 mo	Recovered	Kuijper E.J., 1992
M/41	None	Dental	Convulsion	Left frontoparietal region		Actinomyces	Chlo	6 wks	Recovered	Zijlstra E.E., 1992
M/19	None	Dental	Headache, vomiting, right sided weakness	Left parietal region	Single		Chlo + Cefo	10 wks	Recovered	Renton T.F., 1996
M/47	Alcohol abuse	Dental	Headache, vomiting, left sided weakness	Right occipital lobe	Single		Ceftriaxon	4 wks	Recovered	Stepanovic S., 2005

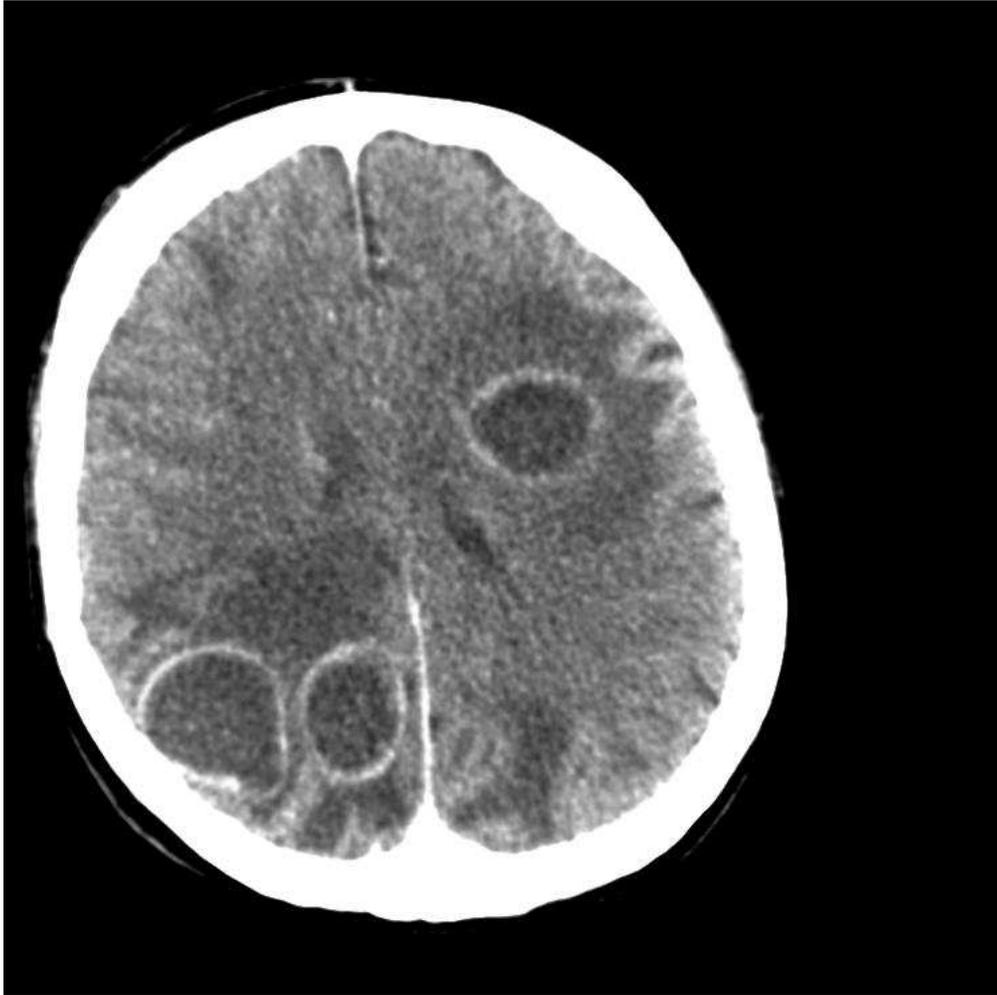
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sex/age (yr)	underlying illness	source	presenting symptoms	localisation	infection	mixed with	antibiotic treatment	duration	outcome	author/year
M/62	Carcinoma left ear	Otogenous	Drainage left ear, confusion	Posterior inferior temporal region	Single		Pen + Chlo +Co	3 wks (until death)	Died	Martin B.F., 1967
M/31	None	?	Right hemianopsia	Left parietal-occipital	Single		Amp + strep	2 wks	Recovered	Burgher L.W.,1973
?	?	?			Single		?	?	?	Brewer, 1975
?	?	?				?	?	?	?	Brewer, 1975
M/34	None	Dental	Headache, vomiting	Left frontal region		Anaerobic streptococci, Fusobacterium polymorphum, Bacteroides melaninogenicus, S. milleri	Amp + Ge + Me	?	Recovered	Ingham H.R., 1978
F/7	Cyanotic congenital heart disease	?	Headache, irritability	Left frontal region	Single		Clo	At least 4 wks	Recovered	Garner J.G., 1979
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M/19	None	Dental	Headache, vomiting, right sided weakness	Left parietal region	Single		Chlo + Cefo	10 wks	Recovered	Renton T.F., 1996
M/47	Alcohol abuse	Dental	Headache, vomiting, left sided weakness	Right occipital lobe	Single		Ceftriaxon	4 wks	Recovered	Stepanovic S., 2005

Table I. Reported cases of cerebral abscesses due to infection with *A. actinomycetemcomitans*.

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