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Original article

High incidence of drug fever due to antibiotics used in treatment of brain abscess in children

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Background: Brain abscess is not uncommon in Thailand. Treatment of brain abscess consists of surgery and antibiotics using high dose and long duration. The problem of drug fever in the treatment of brain abscess has never been reported in children.
Objective: To review the epidemiology of drug fever in children with brain abscess.
Methods: Seventy-five infants and children with brain abscess were analyzed retrospectively.
Results: The mean age was 7.9 ± 4.4 years. The male-to-female ratio was 1.3:1. The most common predisposing factor was congenital heart disease. The most common organisms in congenital heart disease and chronic otitis media were *Streptococci* and *Proteus* respectively. The overall mortality rate was 2.6 %. The incidences of drug fever in the antibiotic regimens using penicillin plus chloramphenicol, cefotaxime plus metronidazole and regimens with cloxacillin were 44.9, 30.8 and 50.0 %, respectively. The overall incidence of drug fever was 38.7 %. The mean onset of drug fever was after 19.4 ± 6.3 days. Most of the patients also had at least one allergic drug reaction such as drug rash, eosinophilia and neutropenia (93.1 %).
Conclusions: There were high incidences of drug fever in all of the existing regimens.

Keywords: Brain abscess; chronic otitis media; congenital heart disease; drug fever.

Brain abscess is a disease that consists of localized free or encapsulated pus within the brain substance [1]. Brain abscess is not uncommon in Thailand and causes significant mortality and morbidity. Empiric antibiotics recommended previously were penicillin and chloramphenicol administered intravenously in doses appropriate for meningitis [2, 3]. We had used this regimen before 1998. There had been a number of drug fevers leading to the change of antibiotics. After 1998, the new initial empiric antibiotics recommended were the third generation cephalosporins and metronidazole [4]. We have used this new regimen since that time. Drug fevers still occurred. The exact incidence of drug fevers remains unknown. It has been estimated to occur in approximately 10 % of inpatients [5]. To our knowledge, there is no report of the incidence of drug fevers in children. The objective of this study is to review our experience.

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Materials and methods

We retrospectively collected medical records of pediatric patients with brain abscesses admitted to the Division of Pediatric Neurology, from January 1985 to December 2006, at Srinagarind Hospital which is the referral center for northeast Thailand.

Inclusion criteria for brain abscess

We used the followings:

1. Age below 15 years.
2. Diagnosis of brain abscess by cranial CT or magnetic resonance images (MRI) with localized brain parenchymal lesions with perilesional brain edema and postcontrast ring enhancement, associated with at least one of the following findings: positive cerebrospinal fluid (CSF) culture of purulent material aspirated from intracerebral lesions during operation, histology suggesting brain abscess, or strong clinical evidence including typical manifestations and improvement after antibiotic treatment [6].
3. For the nonsurgically treated patients, the criterion was a CT or MRI with improvement after antibiotic treatment [7].
4. Completely followed until discharge.

Exclusion criteria for brain abscess

We used the followings:

1. No or incomplete medical record.
2. Subdural empyema and epidural abscesses.
3. Uncertain diagnosis.
4. Incompletely followed until discharge.

We collected the following data: age, sex, predisposing factors and causative organisms. Details of treatment such as surgical treatment, antibiotics, drug fever and allergic reactions were recorded.

Drug fever

We diagnosed drug fever by the following criteria [5, 8-10].

1. Obscure fever with negative blood culture and where other explanations for the fever have been excluded.
2. Temperature 102-106 ^{o}F (38.9-41.1 ^{o}C).
3. Relative bradycardia in patients not on -blocker therapy, no arrhythmia, no heart block and no pace maker.
4. Fever occurs despite a patient's clinical improvement. The patients should look relatively well for the degree of fever and do not have shaking chills unless they have been given antipyretics.

We also considered that patients with drug fever:

- May have eosinophilia (>300 eosinophils/mm^3) in peripheral smear [11];
- May be accompanied by neutropenia (<1,500/mm^3) [11];
- May be accompanied by drug rash or urticaria.

The patients were diagnosed as drug fever when they had criteria 1-4 (see **Table 6**).

Drug hypersensitivity and allergy

Drug hypersensitivity was defined as an immune-mediated response to a drug agent in a sensitized patient [12]. Drug allergy was restricted specifically to a reaction mediated by IgE [12].

Results

General characteristics

We recruited 75 patients. Forty-three patients were male (57.3 %) and 32 were female (42.7 %). Male-to-female ratio was 1.3:1. Their ages ranged from 2 months to 14.8 years (7.9 ± 4.4 years). There were 4 patients younger than 1 year-old (5.3 %).

Predisposing factors and bacteriology

Congenital heart diseases and chronic otitis media were the most common predisposing factors, accounting for 54 patients (72 %). Other predisposing factors are shown in **Table 1**. We could not find predisposing factors in 16 patients (21.3 %).

Table 1. Predisposing factors for development of brain abscess in 75 patients.

Predisposing factor	Number of cases (%)
Congenital heart diseases (CHD)	38 (50.7)
Cyanotic congenital heart diseases	*36 (48.0)*
Tetralogy of Fallot (TOF)	26 (34.7)
Transposition of great vessels (TGV)	3 (4.0)
Double outlet right ventricle (DORV)	2 (2.7)
Truncus arteriosus	2 (2.7)
Tricuspid atresia	1 (1.3)
AV canal	1 (1.3)
Complex heart disease	1 (1.3)
Acyanotic congenital heart diseases	*2 (2.7)*
Atrial septal defect (ASD)	1 (1.3)
Endocardial cushion defect	1 (1.3)
Chronic otitis media (COM)	16 (21.3)
Unknown	16 (21.3)
Oral infection	2 (2.7)
Meningitis	2 (1.3)
Nasal septal abscess	1 (1.3)

Most cases of congenital heart diseases were cyanotic (94.7 %) such as tetralogy of Fallot (TOF) (68.4 %). The most common organisms were *Streptococci* of various species, both aerobes and anaerobes (35.7 %). In chronic otitis media, most organisms were gram negative bacilli (81.3 %) and the most common were *Proteus* and *Pseudomonas aeruginosa* (50.0 and 12.5 % respectively). Only 2 cases were anaerobes *(Peptostreptococcus)* (12.5 %) (**Table 2**). In 16 patients with unknown sources and 5 miscellaneous sources, there were multiple other organisms (**Table 2** and **3**).

Management and outcome

The management and outcome are summarized in **Table 4**. Management included antibiotics with or without aspiration, excision, or both. We used antibiotics only in patients with multiple abscesses, small abscess (<2.5 cm.), or abscess in vital area. The overall mortality rate was 2.6 %. One patient died because of postoperative hemorrhage.

Table 2. Organisms of brain abscesses in congenital heart disease, chronic otitis media, and unknown sources.

Congenital heart diseases (n=38)		**Chronic otitis media (n=16)**		**Unknown sources (n=16)**	
Organisms	Number (%)	Organisms	Number (%)	Organisms	Number (%)
Streptococci	15 (35.7)	*Proteus* spp.	8 (50.0)	*Staphylococcus aureus*	2 (12.5)
Microaerophilic	5 (11.9)	*Proteus mirabilis*	4 (25.0)	*Microaerophilic streptococcus*	2 (12.5)
Peptostreptococcus	2 (4.8)	*Proteus vulgaris*	4 (25.0)	*Staphylococcus epidermidis*	1 (6.3)
α-streptococcus	2 (4.8)	*Pauruginosa*	2 (12.5)	*Streptococcus* spp.	1(6.3)
β-streptococcus	2 (4.8)	*Peptostreptococcus*	2 (12.5)	*Gardnerella vaginalis*	1 (6.3)
γ-streptococcus	2 (4.8)	*Escherichia coli*	1 (6.3)	*Peptostreptococcus* spp.	1 (6.3)
Group D	1 (2.4)	*Citrobacter diversus*	1 (6.3)	*Kingella denitrificans*	1 (6.3)
Bovis	1 (2.4)	*Morganella morganii*	1 (6.3)	No growth	4 (25.0)
Diptheroids	2 (4.8)	No growth		No surgery	3 (18.8)
Fusobacterium	1 (2.4)				
Bacteroides spp.	1 (2.4)				
Bacillus spp.	1 (2.4)				
Hemophilus influenzae	1 (2.4)				
Pseudomonas fluorescens	1 (2.4)				
No growth	18 (42.9)				
No surgery	2 (4.8)				

*Two patients had two bacteria isolated, one had three bacteria isolated.

Table 3. Organisms in 5 patients with miscellaneous sources.

Predisposing factor	**Organisms**
Meningitis	*Citrobacter freundii*
Meningitis	No growth
Oral infection	No growth
Oral infection	*γ-hemolytic streptococcus*
Nasal septal abscess	*Staphylococcus aureus*

Table 4. Summary of management and outcome in 75 cases.

Treatment	**Number of patients**	**Survival (%)**	**Death (%)**
Aspiration	39 (52.0)	38 (97.4)	1 (2.6)
Aspiration and excision	16 (21.3)	16 (100)	0 (0)
Excision	10 (13.3)	10 (100)	0 (0)
Medical treatment only	10 (13.3)	10 (100)	0 (0)
Total	***75 (100)***	***74 (98.7)***	***1 (2.6)***

Drug fever

We have administered high doses of antibiotics as recommended for the treatment of meningitis: penicillin G 300,000-400,000 U/kg/day, chloramphenicol 100 mg/kg/day, metronidazole 30 mg/kg/day, cefotaxime 200-300 mg/kg/day and cloxacillin 300-400 mg/kg/day for 4-8 weeks. The majority antibiotics used were penicillin G plus chloramphenicol and cefotaxime plus metronidazole (65.3 and 17.3 %, respectively). We found a high incidence of drug fever in both regimens (44.9 % and 30.8 %, respectively). We used cloxacillin alone in three patients and all developed drug fever (100 %). There was no drug fever in three patients who received cloxacillin plus chloramphenicol. So the incidence of drug fever in the regimen with cloxacillin was 50 %. The overall incidence of drug fever for all groups was 38.7 %. The onset of drug fever was 3 weeks into the regimens with penicillin plus chloramphenicol and cefotaxime plus metronidazole; and 9 days in the cloxacillin group (**Table 5**). We recorded other reactions in all of the patients that had drug fever. Most had at least one of the followings: 1) drug rash, 2) eosinophilia, 3) neutropenia, 4) a confirmed decrease in the temperature to normal 72 hours after discontinuing the antibiotics (**Table 6**). Only two patients had no other reaction than fever. We diagnosed drug fever by strictly following the other criteria for drug fever.

Discussion

Brain abscess is not uncommon at our hospital. The average age and sex were similar to other studies [13-15]. Congenital heart disease was the most common predisposing factor as in other studies [12-14]. But we found a high incidence of chronic otitis media (21.3 %) which was higher than in studies by Ciurea *et al* [13], Ratanasiri *et al* [14], and Wong *et al* [15] (10.17 %, 12.9 % and 6 %, respectively). This finding was due to the poor socioeconomic status of our patients that usually neglected treating chronic otitis media for years. The most common organisms in the patients with congenital heart diseases were *Streptococci* of various species, both aerobes and

Table 5. Antibiotics used and drug fever in 75 cases.

Antibiotics	Number of cases (n=75)	Drug fever Number of cases (%)	Date of drug fever Days (Mean ± SD)
Penicillin G + chloramphenicol	49 (65.3)	22 (44.9)	9-39 (20.5 ± 5.7)
Cefotaxime + metronidazole	13 (17.3)	4 (30.8)	21-22 (21.7 ± 0.6)
Cefotaxime + chloramphenicol	2 (2.7)	0 (0)	-
Cefotaxime	1 (1.3)	0 (0.0)	-
Cloxacillin	3 (4.0)	3 (100)	5-14 (9.0 ± 4.6)
Cloxacillin + chloramphenicol	3 (4.0)	0 (0)	-
Cloxacillin + metronidazole	1 (1.3)	0 (0)	-
Ampicillin + metronidazole	1 (1.3)	0 (0)	-
Ampicillin + chloramphenicol	1 (1.3)	0 (0)	-
Cotrimoxazole + metronidazole	1 (1.3)	0 (0)	-
Total	***75 (100)***	***29 (38.7)***	***5-39 (19.4 ± 6.3)***

Table 6. Other reactions in 29 patients with drug fever.

Allergic reactions	Number of cases (%)
Drug rash	9 (32.1)
Drug rash + eosinophilia + neutropenia	6 (21.4)
Drug rash + neutropenia	5 (17.9)
Eosinophilia	3 (10.7)
Drug rash + eosinophilia	2 (7.1)
Neutropenia	2 (7.1)
None	2 (7.1)

anaerobes (35.7 %). This finding is similar to the report by Saez-Llorens *et al* [16]. In chronic otitis media, the most common organism is *Proteus* which is similar to the report by Sennrogu *et al* [17]. The mortality rate of our study was low because of accessibility of early neurosurgical treatment. In the patients with large single abscess, aspiration without excision was selected. Excision was carried out when possible. Medication alone was used in the abscess that was located in vital areas.

We noted a high incidence of drug fever in our study (38.7 %). Hypersensitivity is the most common cause of drug fever [18]. It is estimated that truly allergic reactions occur in about 5 % of all treatments [19]. The overall incidence of penicillin-related drug allergy is 2 % [20]. We think the drug fever in our patients is a hypersensitivity reaction because most of them had fever accompanied with rash, eosinophilia or neutropenia. We did not discontinue antibiotics immediately after we suspected drug fever but we waited until there was other evidence to exclude infection or other causes. We were sure that all of our patients were true cases of drug fever. We think that the high incidence was due to the higher doses and longer durations of antibiotics administered in brain abscess than in other diseases. To our knowledge, there is no previous report about the incidence of drug fever in the treatment of brain abscess. Oizumi *et al* [21] had reported drug fever induced by parenteral antibiotics in adults with various diseases but not in brain abscess. The incidence with drug fever of cefotaxime was 15 %. There were no cases of drug fever in penicillin plus chloramphenicol or cefotaxime plus metronidazole in his study. The mean onset of drug fever in the patients who received penicillin plus chloramphenicol and cefotaxime plus metronidazole was after about 3 weeks. This finding suggests that the mechanism of drug fever is delayed type hypersensitivity.

Before 1998, we had used penicillin plus chloramphenicol as initial empiric antibiotics. Penicillin had been the mainstay of therapy due to its excellent activity against streptococci and most anaerobic bacteria. Chloramphenicol was often administered concurrently with penicillin because of the high lipid solubility which results in excellent central nervous system penetration and the activity against anaerobic bacteria [3]. Chloramphenicol has fallen out of favor because of its lack of bactericidal activity for certain organisms, association with idiosyncratic aplastic anemia, and increasing bacterial resistance. [22] After we found a high incidence of drug fever, we used cefotaxime plus metronidazole since 1998. Cefotaxime has the advantage because it is a bacteriocidal and achieves adequate minimum inhibitory concentration in brain abscess for a variety of pathogens. Metronidazole has an excellent brain abscess cavity penetration and it is bacteriocidal against strict anaerobes. The incidence of drug fever in this new regimen is still high (30.8 %). Jansson *et al* [23] reported the efficacy and safety of cefotaxime in combination with metronidazole for empirical treatment of brain abscess in 66 cases. He found that there were adverse reactions leading to discontinuation of cefotaxime that occurred in 38 patients (57.6 %). But this report did not mention drug fever.

We often have to discontinue these antibiotics before the end of their courses. We thus have to find new regimens. The properties of new antiobiotics should include good penetration into brain tissue, low incidences of drug allergy and should cover *Streptococci* (aerobes and anaerobes) and gram negative bacilli which together are the majority of organisms in brain abscess. Antibiotics that have good penetration into brain tissue are cefotaxime, ceftazidime, ceftriaxone, chloramphenicol, ciprofloxacin, clindamycin and metronidazole [24]. According to our study, cefotaxime, chloramphenicol and metronidazole were found to have a high incidence of drug fever. Ceftazidime, ceftriaxone, ciprofloxacin and clindamycin have not been studied for drug fever. Vancomycin has fair penetration into brain tissue [24] but there has been a lower incidence of drug fever compared to cloxacillin. We propose other choices for initial empiric antibiotics in various predisposing factors for study:

1. In congenital heart disease, *Streptococci* both aerobes and anaerobes are the most common organisms. Third generation cephalosporins such as ceftriaxone or ceftazidime plus clindamycin need to be evaluated.
2. In chronic otitis media, gram negative bacilli especially *Proteus* and *Pseudomonas* and anaerobic bacteria are the most common organisms. Ceftazidime or ciprofloxacin plus clindamycin need to be evaluated.
3. In penetrating trauma or facial infection, *Staphylococci* are the most common organisms. Vancomycin plus third generation cephalosporins need to be studied. Cefotaxime plus metronidazole also need further study since there were only 17 patients in our study.

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