Objective: To evaluate prevalence, age, position, predisposing factors, bacteriology, clinical features and outcomes of children with subdural empyema (SDE) and brain abscess (BA).

Design: Retrospective hospital-based study in a tertiary children’s hospital.

Methods: Clinical data were reviewed on all children classified as having SDE or BA for 10.75 years from 1 January 1992 to 31 August 2003 at the Royal Alexandra Hospital for Children, Sydney, Australia.

Results: Forty-six children with intracranial suppuration were identified: 26 had BA, 16 had SDE and four children had both SDE and BA.

Significant differences between SDE and BA were that: sinusitis was a predisposing factor for SDE \((P = 0.01)\), *Streptococcus milleri* was the main organism isolated in SDE \((P = 0.02)\), periorbital oedema \((P = 0.005)\) and photophobia \((P = 0.02)\) were clinical features specifically associated with SDE, and 75% of multiple abscesses were in females \((P = 0.005)\).

The age distribution of SDE was biphasic, with peaks at <2 years and >7 years. Cases of BA peaked at age 9–11 years. Forty-eight per cent of all children were between 9 and 13 years old; 20% were <1 year old. All the children with SDE and BA were aged 1 year or less.

Three of the 46 children died, all with BA. Eighteen (39.1%) returned to normal and 25 (54.3%) had neurological complications. Neurological complications were more common in the BA group.

Conclusion: The mortality rate of intracranial suppuration is low, but morbidity remains high. A high degree of suspicion is needed to diagnose and treat intracranial infections early.

Key words: brain abscess; children; sinusitis; subdural empyema.

PATIENTS AND METHODS

We included all patients classified as having an SDE or BA at the RAHC from 1 January 1992 to 31 August 2003. The Medical Records ICD-9 codes utilized were 324.0 and 324.9 from 1992 to 1998 and G06.2 and G06.0 from 1998 to 2003. Extrudal empyema was classified using different codes and so was not seen in our study. Using a pre-designed and piloted proforma, we collected data from the medical records on the specific organisms, position of abscess, predisposing factors, clinical features, treatments and outcomes of patients. The parameters for the data to be collected were created by reviewing previous published studies.\(^1\)\(^\text{-}^{12}\)

The data were analysed using the SPSS program. A chi-squared analysis was used to compare gender and number of abscesses and Fisher’s exact test was used to compare the other parameters evaluated for significance.

Children’s Hospital at Westmead (CHW) Clinical Ethics Committee approval was obtained before commencement of this study.

RESULTS

Fifty-one children were recorded to have had SDE or BA. Five of these children were excluded, one because the medical records could not be found, and four others had been misclassified. The first had a subdural haemorrhage, not an empyema. In the second, abscess was part of the differential diagnosis, not the final diagnosis. The third had a lower spinal cord epidural abscess and the fourth had encephalomyelitis, not an abscess.

The final study size was 46 children, of whom 26 had BA, 16 had SDE and four had both SDE and BA. The predisposing factors for the last four children were neurosurgery and meningitis, meningitis, trauma and the final child had no known predisposing factors.

Age

The age range for these children was from 1 month to 16 years. Forty-eight per cent of children were between 9 and 13 years of age; 20% were <1 year old. All the children with both BA and SDE were aged 1 year or less. Subdural empyema had a biphasic distribution: four children were <2 years old and the rest were >7 years old. BA children were evenly distributed through the age range with a peak at 9–13 years (Fig. 1).

The mean (SD) and median ages are as follows: BA \((n = 26)\): 97.7 (56.7) and 108 months; SDE \((n = 16)\): 94.4 (61.7) and 115 months; SDE and BA \((n = 4)\): 7.3(4.1) and 7.5 months; all \((n = 46)\): 88.7 (60.9) and 108 months. The mean and median age of SDE and BA was significantly lower than for either BA or SDE alone \((P < 0.01)\).
Gender

Thirty (65.2%) of the children were boys (61.5% of BA and 68.8% of SDE), giving an M:F ratio of 1.9:1.

Origin of patients

Twelve of the 46 children were flown in from overseas, mostly from Noumea.

Annual distribution

The annual distribution of cases remained constant, with no statistically significant variation over time by Poisson distribution.

Bacteriology

The most common organisms isolated from abscesses were *Streptococcus milleri* (17.4%), which was significantly more common (37.5%) in children with SDE ($P = 0.02$), and *Streptococcus pneumoniae* (17.4%), which was evenly distributed between children with SDE and with BA. There were seven isolates of *Staphylococcus aureus* (15.2%), with three of the seven being methicillin resistant (MRSA). *Proteus* was isolated from five children (10.9%), more commonly from those with BA (four BA and one BA + SDE). Other organisms detected included *Haemophilus influenzae*, *Pseudomonas* and *Aspergillus* (three cases of each), *Escherichia coli* and *Bacteroides* (two cases) and *Candida* and *Streptococcus mitis* (one case each). Gram-negative organisms were more commonly found in BA. *Aspergillus* was only seen in cases of BA (Table 1).

Location of abscess or subdural empyema

The location was determined by which lobe the SDE was overlying or the lobe in which the BA was situated.

The frontal lobe was the most common site, with 58% of abscesses/SDE located in this region. The parietal lobe followed with 37%, and then the temporal lobe with 21.7% (Table 2). There is an overlap due to multiple collections in 20 cases. 26.7% of males had multiple collections compared to 75% of females ($P = 0.005$). The odds ratio is 0.12 (95% CI = 0.03–0.487).

Predisposing features

Sinusitis was the most common predisposing factor, and was significantly more common in children with SDE ($P = 0.01$). Sinusitis was found in 59% of those with SDE. Other common predisposing factors included meningitis, otitis and

| Table 1  | Bacteriology of intracranial infections |
|----------|----------------------------------------|
| Organism | BA ($n = 26$) | SDE ($n = 16$) | BA + SDE ($n = 4$) | Significance | Total ($n = 46$) |
|----------|--------------|---------------|-------------------|--------------|-----------------|
| *Streptococcus milleri* | 2            | 6             | 0                 | $P = 0.02$   | 8               |
| *Streptococcus pneumoniae* | 4            | 3             | 1                 | NS           | 8               |
| *Staphylococcus aureus* | 3            | 4             | 0                 | NS           | 7 (MRSA = 3)    |
| Gram-negative bacilli | 9            | 3             | 3                 | NS           | 15              |
| *Aspergillus* | 3            | 0             | 0                 | NS           | 3               |
| *Streptococcus mitis* | 0            | 1             | 0                 | NS           | 1               |
| *Candida* | 1            | 0             | 0                 | NS           | 1               |

BA, brain abscess; MRSA, methicillin resistant; NS, not significant; SDE, subdural empyema.
neurosurgery. There was no significant association between these factors and either BA or SDE. Leukaemia was only seen in children with BA. Mastoiditis and cyanotic congenital heart disease (CCHD) were also more commonly seen in children with BA. There were no statistically significant differences apart from sinusitis (Table 3).

Signs and symptoms

The three most common clinical symptoms of BA and SDE were fever (71.7%), headache (54.3%) and vomiting (45.7%). The incidence of other symptoms was lower. Of the clinical signs, 50% of patients had a decreased level of consciousness and 28.3% had seizures. Five children were comatose (10.9%), and four of the five had a BA. Photophobia and weakness were noted in 13%. Enlarging head was seen in 10.9% of infants and periorbital swelling and behavioural disturbance were also seen in 10.9%. Less common signs included purulent rhinorrhea, visual disturbance, discharging ears, neck stiffness, VI cranial nerve palsy, gait disturbance, ptosis, weakness and papilloedema. All these features were seen equally in both SDE and BA, although periorbital swelling was a significant clinical feature of children with SDE ($P = 0.005$), and photophobia was also significantly associated with SDE ($P = 0.02$).

Duration of symptoms and time to diagnosis

We tried to collect data on the duration of symptoms before presentation and from presentation until diagnosis; however, there was insufficient information recorded in most case notes to allow us to report any meaningful data. Of the children for whom data were recorded, symptoms ranged from <1 day to 3 months before presentation, and the time from presentation to diagnosis ranged from <1 day to 25 days.

Diagnostic work up

32.6% of the patients received a lumbar puncture as part of the diagnostic investigations. Almost half of these were completed before scanning. None of the children who received a lumbar puncture coned. A computed tomography (CT) scan of the head was performed on 95.7% of the children and magnetic resonance imaging (MRI) on 47.8%. Most cases were diagnosed with a single scan. Diagnostic investigations for SDE and BA were similar, although MRI scanning was performed significantly more often for those children who had a suspected BA rather than an SDE ($P = 0.002$).

Therapy

Antibiotic therapy

A wide range of antibiotic regimes was used. Three drugs were given together on average. The most commonly used antibiotic was cefotaxime (69.6%), then metronidazole (52.6%) and vancomycin (43.5%). Flucoxacillin and gentamicin were given together to 34.8% of children, and penicillin was given to 32.6% of children. Antibiotic regimes for SDE and BA were very similar. Vancomycin and flucoxacillin were used more commonly in cases of BA. Clindamycin was more commonly used in SDE and amphotericin and rifampicin were only used in children with BA.

Other drug therapy

Anticonvulsants were given to 58.7% of children, while 37% were given dexamethasone and 4.3% were given mannitol. A further 4.3% were given acetazolamide in an attempt to reduce intracranial pressure. Dexamethasone, mannitol and acetazolamide were all more commonly used in BA.

Surgical therapy

A burr hole drainage was performed in 48% of children (15 BA and seven SDE), while 43.5% had a craniotomy and drainage performed (11 BA and nine SDE). Fine needle aspiration was used in 45.7% of children (15 BA, five SDE and one both). Most children required only a single drainage procedure. Three children underwent a mastoidectomy, and two children had an ethmoidectomy due to osteomyelitis.

Table 2 Lobe containing brain abscess or underlying subdural empyema

| Lobe containing brain abscess or underlying subdural empyema | Cases |
|-------------------------------------------------------------|-------|
| Frontal                                                     | 27    |
| Parietal                                                    | 17    |
| Temporal                                                    | 10    |
| Occipital                                                   | 5     |
| Cerebellum                                                  | 5     |
| Brainstem                                                   | 1     |
| Thalamus/basal ganglia                                      | 1     |

| Predisposing factor | BA ($n = 26$) | SDE ($n = 16$) | BA + SDE ($n = 4$) | Significance | Total ($n = 46$) |
|---------------------|---------------|---------------|-------------------|--------------|-----------------|
| Sinusitis           | 5             | 9             | 1                 | $P = 0.01$   | 15              |
| Postmeningitis      | 4             | 2             | 1                 | NS           | 7               |
| Otitis              | 3             | 4             | 0                 | NS           | 7               |
| Neurosurgery        | 1             | 3             | 2                 | NS           | 6               |
| Leukaemia           | 5             | 0             | 0                 | NS           | 5               |
| Mastoiditis         | 4             | 1             | 0                 | NS           | 5               |
| CCHD                | 5             | 0             | 0                 | NS           | 5               |
| Trauma              | 2             | 2             | 1                 | NS           | 5               |
| VP shunt            | 0             | 3             | 1                 | NS           | 4               |
| Cystic fibrosis     | 1             | 1             | 0                 | NS           | 2               |
| Immunosuppression   | 2             | 0             | 0                 | NS           | 2               |

BA, brain abscess; CCHD, cyanotic congenital heart disease; NS, not significant; SDE, subdural empyema.
Intracranial suppuration

Table 4: Demographic data of children with intracranial infections

|                  | General | SDE (n = 16) | BA (n = 26) | SDE + BA (n = 4) | Total (n = 46) |
|------------------|---------|--------------|-------------|-----------------|---------------|
| Recurrence       |         |              |             |                 |               |
| Males            |         | 11           | 16          | 3               | 30 (65%)      |
| Females          |         | 5            | 10          | 1               | 16 (35%)      |
| Mortality        |         | 0            | 3           | 0               | 3 (6.5%)      |

BA, brain abscess; SDE, subdural empyema.

Recurrent rate

The overall recurrence rate following treatment was 15.2%. There was no significant difference between the recurrence rates for BA and SDE (Table 4).

Outcomes

Three children (6.5%) of the 46 died. The three who died were BA patients: two had leukaemia, with overwhelming abscess formation, and the other had a pontine astrocytoma, as well as an BA (Table 4). Eighteen of the 46 children returned to normal (39.1%) and 25 had neurological complications (54.3%). Only the complications, which developed within 3 months of hospital admission, are noted here. The main neurological complications included hemiparesis (ICA = 34.6%, SDE = 18.75%), seizures (ICA = 23%, SDE = 6.3%), speech and gait disturbances (total = 7). Cognitive disturbance (total = 4), visual (n = 5) and hearing loss (n = 4) were also common (Table 5).

DISCUSSION

Brain abscess and SDE, although very similar in some aspects, vary widely in their predisposing factors, route of infection, bacteriology, ‘at-risk’ age group and neurological outcomes.

Our study found that SDE has sinusitis as its main aetiological factor, with 58.9% of affected children having sinusitis at presentation. Many studies have reported this association.2–5

Table 5: Outcomes in intracranial suppuration

| Outcomes          | BA (n = 26) | SDE (n = 16) | SDE + BA (n = 4) | Total (n = 46) |
|-------------------|-------------|--------------|-----------------|---------------|
| Return to normal  | 10          | 8            | 0               | 18            |
| Died              | 3           | 0            | 0               | 3             |
| Neurological sequelae | 15  | 6            | 4               | 25            |
| Hemiparesis       | 9           | 3            | 1               | 13            |
| New shunt         | 7           | 2            | 1               | 10            |
| Hydrocephalus     | 5           | 2            | 2               | 9             |
| Oedema            | 6           | 1            | 1               | 8             |
| Seizures          | 6           | 1            | 1               | 8             |
| Speech            | 5           | 2            | 0               | 7             |
| Ataxic gait       | 4           | 2            | 1               | 7             |
| Osteomyelitis     | 2           | 4            | 0               | 6             |
| Cognitive problems| 2           | 2            | 0               | 4             |
| Visual disturbance| 2           | 1            | 1               | 4             |
| Hearing disturbance| 0      | 2            | 1               | 3             |
| Change in tone    | 2           | 1            | 0               | 3             |
| Deaf              | 2           | 0            | 1               | 3             |
| Haemorrhage       | 2           | 0            | 1               | 3             |
| Cerebral palsy    | 1           | 0            | 1               | 2             |
| Memory disturbance| 1           | 1            | 0               | 2             |
| Blind             | 1           | 0            | 0               | 1             |
| Infarction        | 1           | 0            | 0               | 1             |

Note. Children often had more than one neurological complication. BA, brain abscess; SDE, subdural empyema.

and Nathoo et al.5 postulated that sinusitis predisposes to SDE due to both direct and indirect methods of spread. The direct method may occur through congenital or traumatic dehiscence, erosion through the posterior wall of the frontal sinus or through existing foramina. Indirect spread is probably more common due to retrograde thrombophlebitis through the interconnected extracranial and intracranial venous systems.1–5

Brain abscess develops in most cases through haematological spread from a remote focus of infection.6,7 In our study, cyanotic congenital heart disease, mastoiditis, leukaemia and meningitis were the most common underlying factors associated with BA.

Predisposing factors have not changed significantly in the last 50 years. A study by Fischer et al., which started evaluating patients in 1945, had as its main predisposing factors: cyanotic heart disease, otitis, sinusitis, head injuries and cystic fibrosis.8 We also found all these factors in our study. Interestingly, in our study there was only a minority of cyanotic congenital heart disease, 10.9%, compared to the 50% found by Fischer et al.8 in 1981. This suggests that prophylactic care against BA in these patients is more effective nowadays.

Male patients dominated in both the BA and the SDE cases. This male predominance has been shown in most studies.3–5,7,9–12 Theories for this include larger sinuses and rapid growth of frontal sinuses in males between 7 and 20 years old and more energetic nose-clearing habits in males.5,11 Most children with SDE were over 7 years old in our study, which would coincide with this suggestion. Interestingly, although male patients dominated, female patients were significantly more likely to have multiple abscesses, with 75% of females having multiple abscesses. This association has not been reported before and, although it was statistically significant, may just be coincidence. It should be looked for in future studies.

The bacteriology of BA and SDE in this study varied widely depending on the underlying surgical or medical conditions, the route of infection and the geographic distribution. Streptococcus milleri and S. pneumoniae were the most common organisms detected, closely followed by S. aureus. Streptococcus milleri was the organism most frequently implicated in relation to SDE in several previous studies.6,12 In a study of brain abscesses in 1999, Fenton et al. suggested that S. milleri had a sinogenic source.10 The association between sinusitis, S. milleri and SDE seen in our study is consistent with this hypothesis.

In 1983, a previous study from RAHC by Sutton and Ouvrier1 found that the frontal lobe was the most common site of BA, followed by the parietal lobes. Our study has found this same distribution, as have many others.3,5,6,9 It is thought that the frontal lobe is affected due to its proximity to the frontal sinuses, and the temporal lobes due to the proximity of the paranasal and sphenoid sinuses.4 Otogenic infections have also been implicated in cerebellar abscesses.

The early recognition of brain abscesses and SDE is a challenge. Although CT and MRI scans have made diagnosis and follow up easier, there still remains a significant delay to diagnosis and treatment, which is thought to contribute to morbidity and mortality.1–5,8,9 It has been suggested that this is due to the fact that abscesses can be asymptomatic until late in their course and that the clinical features of headache, fever, vomiting and altered mental state (which were also seen in our study) are vague non-differentiating signs.4,11 Late features of both ICA and SDE include seizures, hemiparesis and other focal neurological signs, but as abscess is most common in the frontal lobe, the silent area of the central nervous system (CNS) signs can present at an even later point in time.4

In our study the duration of symptoms to presentation ranged from hours to 3 months and presentation to diagnosis was hours to 25 days. Kao et al. in 2003 reported similar timing with
symptoms to hospitalization ranging from hours to 2 months.\textsuperscript{11} Just over 10\% of our patients presented with periorbital cellulitis, which is often not recognized as a sign of underlying sinus disease. If there is evidence of orbital disease, such as proptosis, it is important to image the sinuses as well as the orbit, and to consider the possibility of intracranial extension.\textsuperscript{2–5}

A wide array of therapies was used to treat the patients in this series, although regimes were similar for both SDE and BA. In our study, metronidazole, vancomycin and a third-generation cephalosporin were the typical antibiotics prescribed. This triad was also found to be the most commonly used antibiotic therapy in a study completed by Giannoni et al. \textsuperscript{1997}.\textsuperscript{8} The cephalosporin and metronidazole were also commonly used in many other studies.\textsuperscript{3,6}

Treatment has conventionally been based on early diagnosis, i.v. antibiotics and early neurosurgery, either craniotomy, or burr hole drainage. These treatments were used in all studies.\textsuperscript{1–15,17,18} with only a few small groups trying new therapies such as endoscopic drainage.\textsuperscript{16} However, as well as treating the SDE or abscess it is also important to treat the primary source of infection, either in the sinuses\textsuperscript{17} or elsewhere in the body.\textsuperscript{5,18} Only five (18.5\%) of 27 patients in our study with ENT sepsis had surgical treatment of the primary source. Hoyt and Fisher\textsuperscript{17} found that sinus drainage, performed simultaneously with neurosurgical drainage, significantly reduced the incidence of neurosurgical re-exploration and length of hospitalization, so our patients may have been disadvantaged by the low rate of ENT surgery.

Childhood cancer patients are particularly susceptible to developing BA.\textsuperscript{19} In our study, eight children with cancer developed BA, including the three who died. Six of the eight children with cancer had haematological malignancies. The association between leukaemia and BA was noted in a study by Antunes et al.\textsuperscript{19} in 1998, who reported a poor prognosis for oncology patients who develop BA, particularly those with leukaemia. Oncology patients also show a different spectrum of organisms, to the majority, because of their underlying immunosuppression. Four out of five of the leukaemia patients in our study grew Aspergillus, and in the remaining child no cultures were taken. The other three cancer patients grew Pseudomonas, S. aureus and had negative cultures, respectively.

Mortality for BA was reported as 36\% before 1970 and 14\% by 1981, according to a study completed by Fischer et al.\textsuperscript{9} Mortality has decreased, which has been attributed to better scans, better neurosurgical techniques and more powerful antibiotics, but morbidity still remains significant.\textsuperscript{4,8} Late seizures and hemiparesis were some of the most common neurological sequelae found both in our study and several others.\textsuperscript{9}

\section*{CONCLUSION}

Brain abscess and SDE are rare in Australia, with only four children a year presenting to our tertiary referral centre, over a quarter of whom were transferred from overseas. Therefore, we need a very high degree of suspicion to make an early diagnosis. This paper has shown that sinusitis is the main predisposing factor for SDE, with \textit{S. milleri} the main organism. The age groups we need to be most suspicious of are <2 years and >7 years for SDE and 9–11 years for BA. Being less than 1 year of age is a risk factor for developing both SDE and BA concurrently. We have also shown that males tend to develop more SDE and brain abscesses; however, females are more susceptible to developing these infections at multiple sites. Overall, 54.3\% of children developed neurological complications showing us how serious and life changing these infections can be. The good news is that with newer antibiotics and scanning techniques, plus prompt neurosurgical intervention mortality is decreasing, but larger studies (as the main limitation of our study is its low numbers) and studies into future directions can only benefit us in the future.

\section*{REFERENCES}

1. Sutton DL, Ouvrier RA. Cerebral abscess in the under 6 month age group. \textit{Arch. Dis. Child.} 1983; \textit{58}: 901–5.
2. Brockova J, Rigamonte D. Intracranial empyema. \textit{Pediatr. Infect. Dis. J.} 2000; \textit{19}: 735–7.
3. Gallagher RM, Gross CW, Phillips CD. Suppurative intracranial complications of sinusitis. \textit{Laryngology} 1998; \textit{108}: 1635–42.
4. Giannoni CM, Stewart MG, Alford EL. Intracranial complications of sinusitis. \textit{Laryngology} 1997; \textit{107}: 863–7.
5. Nathoo N, Nadvi SS, van Dellen JR, Gowes E. Intracranial subdural empyemas in the era of computed tomography: A review of 699 cases. \textit{Neurosurgery} 1999; \textit{44}: 529–35.
6. Lu CH, Chang WN, Lin YC et al. Bacterial brain abscesses: Microbiological features, epidemiological trends and therapeutic outcomes. \textit{J. Med.} 2002; \textit{95}: 501–9.
7. Takeshita M, Kagawa M, Yato S et al. Current treatment of brain abscess in patients with cyanotic congenital heart disease. \textit{Neurosurgery} 1997; \textit{41}: 1270–9.
8. Fischer EG, McLennan JE, Suzuki Y. Cerebral abscess in children. \textit{Am. J. Dis. Child.} 1981; \textit{135}: 746–9.
9. Donaldson G, Webster D, Crandon I. Brain abscess at the University hospital of the West Indies. \textit{West Indian Med. J.} 2000; \textit{49}: 212–15.
10. Fenton JE, Smyth DA, Viani LG, Walsh MA. Sinogenic brain abscess. \textit{Am. J. Rhinolaryngol.} 1999; \textit{13}: 299–302.
11. Kao PT, Tseng HK, Liu CP, Su SC, Lee CM. Brain abscess: Clinical analysis of 53 cases. \textit{J. Micro Immunol. Infect.} 2003; \textit{36}: 129–36.
12. Skelton R, Maixner W, Isaacs D. Sinusitis-induced subdural empyema. \textit{Arch. Dis. Child.} 1992; \textit{67}:1478–80.
13. Giannoni C, Sulek M, Friedman EM. Intracranial complications of sinusitis: A paediatric series. \textit{Am. J. Rhinolaryngol.} 1998; \textit{12}: 173–8.
14. Ciurea AV, Stoica F, Vasilescu G, Nuteanu L. Neurosurgical management of brain abscesses in children. \textit{Child. Nerv. Syst.} 1999; \textit{15}: 309–17.
15. Su TM, Lan CM, Tasi YD, Lee TC, Lu CH, Chang WN. Multiloculated pyogenic brain abscess: Experience in 25 patients. \textit{Neurosurgery} 2003; \textit{52}: 1075–80.
16. Fritsch M, Manwaring KH. Endoscopic treatment of brain abscess in children. \textit{Minim. Invasive Neurosurg.} 1997; \textit{40}: 103–6.
17. Hoyt DJ, Fisher SR. Otolaryngologic management of patients with subdural empyema. \textit{Laryngoscope} 1991; \textit{101}: 20–24.
18. Barlas O, Sencer A, Erkan K, Eraksoy H, Sencer S, Bayindir C. Stereotactic surgery in the management of brain abscess. \textit{Surg. Neurol.} 1999; \textit{52}: 404–10.
19. Antunes NL, Haritahan S, DeAngelis LM. Brain abscesses in children with cancer. \textit{Med. Paediatr. Oncol.} 1998; \textit{31}: 19–21.