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Case report

Salmonella brain abscess in a patient on chronic azathioprine therapy for myasthenia gravis: report of an unusual case and review of literature in the postantibiotic era

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Focal intracranial infections caused by *Salmonella* species in adults are exceedingly uncommon. Structural brain injury with coexisting immunocompromised status appears to predispose adults to this rare manifestation of *Salmonella* infection. We report a case of *Salmonella* brain abscess in a patient with myasthenia gravis on chronic azathioprine therapy without any prior structural brain lesion. We reviewed world literature and discuss their analysis of *Salmonella* brain abscess in adult population in the postantibiotic era. *Journal of NeuroVirology (2009) 15, 83–92.*

Keywords: Salmonella; brain abscess; immune compromise; azathioprine; myasthenia gravis

Introduction

Salmonella infection is a public health problem in the United States with more than 40,000 isolates and 133 outbreaks reported to the Centers for Disease Control and Prevention (CDC) in 2006, resulting in a national rate of 13.6 per 100,000 population for 2006 (CDC, 2006). The most commonly reported serotypes are *S. typhimurium*, *S. enteritidis*, *S. newport, and S. heidelberg* (CDC, 2006). Whereas approximately 25% of these isolations are from children less than 5 years, 7.6% of the isolates reported to the CDC were from adults between 50 and 60 years; the incidence is about 10% for each decade of life after 10 years of age (CDC, 2006).

Enterocolitis is the most frequent manifestation of nontyphoidal *Salmonella* infection (Hohmann, 2001). Bacteremia occurs in about 5% (Hohmann, 2001) individuals following oral infection wherein early involvement of the blood stream occurs and gastrointestinal symptoms may be absent. Although *Salmonella* bacteremia can occur in previously healthy children (Tsai and Huang, 2007), immunocompromised status dramatically predisposes adults to nontyphoidal *Salmonella* bacteremia (Gordon, 2008). In the pediatric age group, intracranial *Salmonella* infections such as meningitis, subdural empyema, and brain abscess are not unheard of; they are exceedingly rare in adults. We report what we believe is the first case of *Salmonella* brain abscess in a patient with myasthenia gravis on long-term immunosuppression with azathioprine. Our literature review identified only 24 well-described cases of *Salmonella* brain abscess in adults in the postantibiotic era. In this paper we discuss the results of our analysis.

Case report

A 50-year-old woman presented with a 4-day history of new-onset headache (worse on bending), photophobia, fever and chills, confusion, and new-onset partial seizures with secondary generalization. She was diagnosed with myasthenia gravis 13 years ago. She had failed corticosteroid therapy at that time and subsequently underwent thymectomy a year later. About 10 years ago, she was started on

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immunomodulatory therapy with azathioprine and was currently on 250 mg once a day. Other medical history was significant for poorly controlled diabetes mellitus, hypertension, hyperlipidemia, and hypothyroidism. Three weeks prior to presentation, she had suffered from fever, flu-like symptoms, and self-limiting nonbloody diarrhea. Two of her family members were also affected concomitantly but no workup was done because the illness was self-limiting.

Systemic examination was unremarkable and neurological examination did not reveal any focal neurological deficits. On admission, her white blood cell (WBC) count was $7.6 \times 10^3/mm^3$ and the remainder of the hematologic and comprehensive metabolic panels were unremarkable. Hemoglobin A_{1C} (HbA_{1C}) and erythrocyte sedimentation rate (ESR) were elevated at 10.7% and 105 mm/h, respectively. Her head computed tomography (CT) revealed a right frontal mass lesion. No focal slowing, epileptiform activity, or asymmetry was evident on electroencephalogram, which was reported normal. Cerebrospinal fluid (CSF) analysis was normal. Magnetic resonance imaging (MRI) head scan revealed a well-defined rim-enhancing lesion in the medial frontal gyrus of the right frontal lobe measuring 1.3×1.4 cm in size, with surrounding mass effect and meningeal enhancement without midline shift (Figure 1).

A right frontal craniotomy was performed for exploration of this lesion. Upon dural opening, a clear film of gelatinous material was encountered over the convexity and in continuity with parenchymal abscess located predominantly in the superior frontal gyrus. The gelatinous material was removed via dissection and copious irrigation. Gross purulence was removed along with the abscess capsule from the parenchyma until healthy appearing white matter was encountered. The excised material was sent for histopathologic evaluation and aerobic as well as anaerobic culture. Anaerobic cultures grew chloramphenicol-sensitive *Salmonella heidelberg*. Several blood cultures and CSF cultures were negative for any growth. Postoperatively, patient recovered well and completed a 6-week course of ciprofloxacin and metronidazole. At 3 months follow up, she was asymptomatic and repeat head CT scan demonstrated adequate healing without evidence of abscess recurrence in the same region.

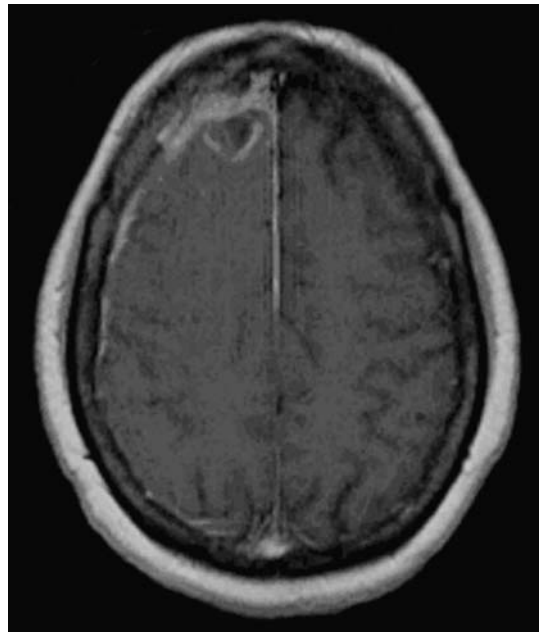

Figure 1 Contrast-enhanced MRI brain demonstrating rim-enhancing lesion in the superior right frontal lobe along with adjacent meningeal enhancement.

Results

A large series by Cohen *et al* (Cohen *et al*. 1987) illustrated that immunosuppression and underlying structural abnormalities predispose to focal *Salmonella* infections. We reviewed medical literature in the postantibiotic era and identified 24 cases of *Salmonella* brain abscess in adult population (Table 1). Results of our review are summarized in Table 2.

In order of frequency, the most commonly reported symptoms included fever (60%), headache (60%), confusion (48%), and seizures (28%). Forty-eight percent of cases, including our case, had prior gastrointestinal symptoms. We identified evidence of immunocompromised status in 72% of the reported cases and many of these patients had more than one reason for immunosuppression. Our patient had a history of immunosuppression secondary to the use of azathioprine. Sixty-four percent of the patients had evidence of prior structural brain damage. Of these, the most commonly identified reason for breach in structural integrity was intracranial malignancy in 36% of cases (primary or metastatic). Other causes such as prior contusion (Fraimow *et al*. 1990), endovascular coiling (Kirollos *et al*. 2002), cerebrovascular accident (Arentoft *et al*. 1993), and hematoma (Chadwick *et al*. 2004) were also identified in these patients.

Culture of either aspirated brain tissue or brain tissue obtained on autopsy was performed in 20 out of 25 cases. These were positive for the organism in all 20 cases (100%). Blood cultures were performed in 20 of the 25 cases. Cultures were positive for the organism in 9 (45%) and negative in 11 (55%) patients. Stool cultures were performed in 17 of the 25 cases. These were positive for the organism in 9 (53%) and negative in 8 (47%) patients. CSF cultures were performed in 15 of the 25 cases and these were positive for the organism in 7 (47%) and negative in 8 (53%) patients.

Table 1 Clinical features of 25 patients with *Salmonella* brain abscess

No.	Age/ Gender	Predisposing conditions leading to possible immunocompromise	Presence of structural brain lesion	Location, number and associated lesions	Presenting symptoms	History pertaining to *Salmonella* infection	Culture results	Surgical drainage/ Biopsy	Medical management	Neurologic outcome	Reference
1	50/F	Azathioprin, uncontrolled DM, thymectomy	None	R Frontal, single	Headache, fever, confusion, seizure	Antecedent diarrheal illness 2 weeks prior	**CSF:** No growth **Brain Tissue:** *Salmonella heidelberg* **Blood:** No growth **Stool:** NA	Yes	Ciprofloxacin, metronidazole	Improved	Present case
2	29/F	Sickle cell disease	None	L Frontal, single	Headache, fever	None	**CSF:** No growth **Brain Tissue:** *Salmonella enteritidis* PT 8 **Blood:** NA **Stool:** NA	Yes	Ceftriaxone	Improved	Karuvath, 2008
3	54/M	DM, alcoholic liver disease, pulmonary tuberculosis	L frontal hematoma drainage 6 months ago	L Parietal, single	Fever, confusion	No diarrhea, but had banding of esophageal varices	**CSF:** NA **Brain Tissue:** *Salmonella typhimurium* **Blood:** NA **Stool:** NA	Yes	Ceftriaxone	Died	Chadwick, 2004
4	46/F	Postoperative corticosteroids for 13 days, status post craniopharyngioma resection	Surgical resection of craniopharyngioma 13 days prior	R Frontal, single (single abscess with empyema)	Headache, confusion	None	**CSF:** NA **Brain Tissue:** *Salmonella enteritidis* **Blood:** NA **Stool:** *Salmonella enteritidis* *Right hip septic arthritis, synovial fluid also grew *Salmonella enteritidis*	Yes	Ciprofloxacin, chloramphenicol	Improved	Schroder, 2008
5	55/F	None	Endovascular coiling of right paraopthalmic aneurysm 3 years ago, regrowth in aneurismal remnant detected 6 months later	R Frontal, single (around coiled aneurysm)	Headache, fever, vomiting, meningism	History of *Salmonella* bacteremia 1 month prior	**CSF:** *Salmonella* group D **Brain Tissue:** NA **Blood:** *Salmonella* group D **Stool:** *Salmonella* group D	No	Ceftrixone, cephalexin	Improved	Kirollos, 2002
6	58/F	None; occult GBM	Occult GBM, L frontal	L Frontal, single (within neoplastic tissue)	Fever, hemiparesis, III CN palsy, somnolence, neck rigidity	None	**CSF:** NA **Brain Tissue:** *Salmonella enteritidis* **Blood:** No growth **Stool:** No growth	Yes	Ceftazidime	Died	Sarria, 2000

Table 1 (*Continued*).

No.	Age/ Gender	Predisposing conditions leading to possible immunocompromise	Presence of structural brain lesion	Location, number and associated lesions	Presenting symptoms	History pertaining to *Salmonella* infection	Culture results	Surgical drainage/ Biopsy	Medical management	Neurologic outcome	Reference
7	59/M	Postoperative corticosteroids for 3 weeks, status post resection of metastatic adenocarcinoma of lung	Resection of metastatic adenocarcinoma of lung 3 weeks prior, L frontal	L Frontal, single	Headache, fever, confusion, seizure, III CN palsy, VII CN palsy, aphasia	None	**CSF:** No growth **Brain Tissue:** *Salmonella typhimurium* **Blood:** No growth **Stool:** No growth	Yes	Ceftazidime, metronidazole, vancomycin	Improved	Kumari, 2000
8	43/M	None	None	R Parietal, single	Headache, fever, confusion, hemianopia	Diarrheal illness 12 days prior during travel to India	**CSF:** *Salmonella enteritidis* **Brain Tissue:** NA **Blood:** *Salmonella enteritidis* **Stool:** *Salmonella enteritidis*	No	Cefotaxime, ciprofloxacin	Improved	Bonvin, 1998
9	56/M	None	None		Fever, confusion, septicemia	Diarrheal illness 2 days prior	**CSF:** No growth **Brain Tissue:** NA **Blood:** *Salmonella typhimurium* **Stool:** *Salmonella typhimurium*	No	Amoxicillin, ofloxacin	Improved	Broux, 1998
10	59/M	DM	Mycotic aneurysm of R cervical artery, embolic stroke 1 month prior (location unknown)	R Frontal, R Temporal, multiple	Fever, right lateral cervical mass (carotid mycotic aneurysm)	Diarrheal illness during hospital stay, cholelithiasis, adenocarcinoma of gall bladder	**CSF:** NA **Brain Tissue:** NA **Blood:** No growth **Stool:** *Salmonella enteritidis* **Bile:** *Salmonella enteritidis*,	No	Cefotaxime, metronidazole	Improved	Lloret, 1996
11	34/?	HIV, CD4 = 20	None	Parietal-occipital, cerebellum, multiple	Fever, seizures	None	**CSF:** NA **Brain Tissue:** *Salmonella typhimurium* **Blood:** No growth **Stool:** No growth	Yes, (stereotactic biopsy)	Amoxicillin, cotrimoxazole, thiamphenicol, ofloxacin	Improved	Smail, 1996
12	34/M	HIV, CD4 = 79	None	R Parietal, multiple	Confusion, seizures, left hemiparesis	None	**CSF:** No growth **Brain Tissue:** *Salmonella typhimurium* **Blood:** No growth **Stool:** No growth	Yes, (stereotactic biopsy)	Cefotaxime, pefloxacin	Improved	Gueit, 1996

Table 1 (*Continued*).

No.	Age/ Gender	Predisposing conditions leading to possible immunocompromise	Presence of structural brain lesion	Location, number and associated lesions	Presenting symptoms	History pertaining to *Salmonella* infection	Culture results	Surgical drainage/ Biopsy	Medical management	Neurologic outcome	Reference
13	49/F	Postoperative corticosteroids for 14 days, status post resection of astrocytoma on corticosteroids	Resection of astrocytoma 14 days prior, R parietal	R Parietal, single (also had overlying empyema)	Fever, confusion	None	**CSF:** *Salmonella enteritidis* **Brain Tissue:** *Salmonella enteritidis* **Blood:** *Salmonella enteritidis* **Stool:** No growth	Yes	Cefotaxime, gentamicin	Improved	Fiteni, 1995
14	24/M	Postoperative corticosteroids, status post resection of glioblastoma on corticosteroids	Resection of glioblastoma, L temporal	L Temporal, single	Fever, confusion	None	**CSF:** *Salmonella enteritidis* **Brain Tissue:** *Salmonella enteritidis* **Blood:** *Salmonella enteritidis* **Stool:** No growth **Bile:** No growth	Yes	Cefotaxime, ofloxacin	Unknown	Bossi, 1993
15	59/M	Chronic renal failure; corticosteroids for preceding 12 days	Hemorrhagic stroke 12 days ago	R Frontal, R Parietal, multiple (within hematoma)	Seizures	Diarrheal illness	**CSF:** NA **Brain Tissue:** Gram; no growth rods (presumed *Salmonella* sp.) **Blood:** *Salmonella typhimurium* **Stool:** *Salmonella typhimurium*	No	Ampicillin, gentamicin	Died	Arentoft, 1993
16	47/M	HIV, CD4 = unknown	Prior contusion in right frontal region, 23 months prior	R Frontal, single	Headache, fever, confusion, seizure	None	**CSF:** *Salmonella enteritidis* **Brain Tissue:** *Salmonella enteritidis* **Blood:** *Salmonella enteritidis* Stools: *Salmonella enteritidis*	Yes	Ampicillin, TMP-SMX, chloramphenicol	Died from unrelated condition	Fraimow, 1990
17	18/M	None	R STA-MCA anastomosis, 4 months prior	R Parietal, multiple	Headache, vomiting, papilledema	None	**CSF:** NA **Brain Tissue:** *Salmonella typhimurium* **Blood:** Positive titers for O and H antigens; no growth blood cultures **Stool:** NA	Yes	NA	Improved	Nagaraja, 1988

Table 1 (*Continued*).

No.	Age/ Gender	Predisposing conditions leading to possible immunocompromise	Presence of structural brain lesion	Location, number and associated lesions	Presenting symptoms	History pertaining to *Salmonella* infection	Culture results	Surgical drainage/ Biopsy	Medical management	Neurologic outcome	Reference
18	18/M	Heredofamilial spinocerebellar degeneration	None	R Fronto-parietal, single	Headache, hemiparesis, vomiting, papilledema, dysphagia	History of "enteric fever" 4 months ago	**CSF:** NA **Brain Tissue:** *Salmonella typhimurium* **Blood:** No growth **Stool:** NA	Yes	Ampiciliin, cotrimoxazole	Improved	Nagaraja, 1988
19	78/M	Corticosteroids for 6 weeks for presumptive metastatic lesions which was confirmed to be GBM on autopsy	Suspected metastasis in L occipital lobes (these were confirmed to be GBM on autopsy)	L Occipital, multiple	Fever, confusion, seizures, meningeal signs	None	**CSF:** *Salmonella enteritidis* **Brain Tissue:** NA **Blood:** *Salmonella enteritidis* **Stool:** NA	No	Cefotaxime, ampicillin, then chloramphenicol	Died	Noguerado, 1987
20	28/M	Corticosteroids	Metastatic testicular cancer in R Occipital region	R Occipital, single	Headache, vomiting, papilledema	Travel to Mexico, coffee enemas and diarrheal illness	**CSF:** No growth **Brain Tissue:** *Salmonella group D* **Blood:** *Salmonella group D* **Stool:** No growth	Yes	TMP-SMX, chloramphenicol	Unknown	Rodriquez, 1986
21	49/M	Perioperative corticosteroids for 3 weeks	Surgical resection of metastatic squamous cell cancer, R parieto-occipital region	R Parieto-occipital, single	Headache, fever, hemiplegia, hemianopia	Travel to Mexico, coffee enemas and diarrheal illness	**CSF:** NA **Brain Tissue:** *Salmonella dublin* **Blood:** NA **Stool:** *Salmonella dublin* *Surgical flap and sutures—*Salmonella dublin*	Yes	Chloramphenicol	Improved	Grosinger, 1986
22	32/M	Occult astrocytoma	Occult astrocytoma, L temporal region	L Temporal, single	Headache, confusion, somnolence, urinary incontinence, papilledema, hyporeflexia, ankle and knee clonus	None	**CSF:** No growth **Brain Tissue:** *Salmonella typhimurium* **Blood:** Positive titers fro O and H antigens, No growth blood cultures **Stool:** NA	Yes	Chloromycetin	Improved	Sharma, 1986

Table 1 (*Continued*).

No.	Age/ Gender	Predisposing conditions leading to possible immunocompromise	Presence of structural brain lesion	Location, number and associated lesions	Presenting symptoms	History pertaining to *Salmonella* infection	Culture results	Surgical drainage/ Biopsy	Medical management	Neurologic outcome	Reference
23	65/F	DM	None	L Cerebellar, single (detected on autopsy, also had meningitis)	Headache, fever, confusion, neck stiffness, nystagmus, L Horner's syndrome	Diarrheal illness 3 days prior, previous cholecystectomy	**CSF:** *Salmonella typhimurium* **Brain Tissue:** *Salmonella typhimurium* **Blood:** No growth **Stool:** *Salmonella typhimurium*	No	Chloramphenicol (organism found to be resistant), then ampicillin	Died from ruptured mycotic cerebral aneurysm	Ellis, 1981
24	45/F	None	None	R Parietal, single	Headache, seizures, left hemiparesis	History of typhoid fever 33 years ago, possible chronic carrier state	**CSF:** No growth **Brain Tissue:** *Salmonella typhimurium* D2 **Blood:** No growth **Stool:** No growth	Yes	Chloramphenicol, cephalothin	Improved	Suzuki, 1976
25	18/M	None	Cerebral concussion, 4 month ago, location unknown	L Temporal, single	Headaches, nausea and vomiting, confusion, hemiparesis and dysphagia, papilledema	Diarrheal illness 4 m ago	**CSF:** NA **Brain Tissue:** "*Typhoid Bacillus*" **Blood:** NA **Stool:** NA	Yes	NA	Improved	Maroun, 1965

*Presumed *Salmonella* infection; definitive tissue diagnosis unavailable.

Table 2. Results of analysis of *Salmonella* brain abscess in adults in postantibiotic era.

Most frequently reported symptoms	• Fever: 60% (15/25) • Headache: 60% (15/25) • Confusion: 48% (12/25) • Seizures: 28% (7/25)
History of preceding diarrheal illness	• 48% (12*/25) *One patient had *Salmonella* bacteremia (Kirollos, 2002)
Predisposing immunocompromised status (several patients had more than one predisposing factors contributing to immune compromise)	• 72% (18/25) o Corticosteroids 32% (8/25) o HIV: 12% (3/25) o DM: 16% (4/25) o Other: 20% (5/25) o None: 24% (6/25)
Prior structural brain damage	• 64% (16/25)
Location of abscess	• Frontal: 40% (10/25) • Parietal: 36% (9/25) • Temporal: 12% (3/25) • Occipital: 12% (3/25)
Number of abscess	• Single: 76% (19/25) • Multiple: 28% (7/25)
Cultures	• Blood: (Performed in 20/25 cases) o Positive 45% (9/20) o Negative 55% (11/20) • Stool: (Performed in 17/25 cases) o Positive 53% (9/17) o Negative 47% (8/25) • CSF: (Performed in 15/25 cases) o Positive 47% (7/25) o Negative 53% (8/25) • Brain tissue: (Performed in 20/25 cases) o Positive 100% (20/20) o Negative 0% (0/20)
Surgical drainage/biopsy	• 72% (18/25)
Empiric antibiotics alone	• 28% (7/25)
Neurologic outcome	• Surgical drainage with postoperative antibiotics o Improved: 72% (13/18) o Died: 27% (3/18) o Unknown: 11% (2/18) • Empiric antibiotics alone o Improved: 57% (4/7) o Died: 22% (3/7) • Overall o Improved: 68% (17/25) o Died: 24% (6/25) o Unknown: 8% (2/25)

Surgical drainage/stereotactic biopsy were performed in 18 patients whereas 7 patients received empiric antibiotics alone. Of the 18 patients who underwent surgical drainage and received postoperative antibiotics, 13 (72%) improved, 3 (17%) died, and the outcome of two cases was unclear. Of the 7 patients who did not undergo surgical drainage but only received antibiotics, 4 (57%) improved and 3 died (43%). Overall, 17 out of 25 (68%) patients improved neurologically, 6 out of 25 (24%) patients died, and outcome in 2 cases was unclear. No statistical difference between the two groups was observed using a two-tailed chi-square test (P =.4868). The statistical power available from 25 patients may be too low to meaningfully infer the difference between conservative and surgical management.

Discussion

Commonly reported organisms causing brain abscess in immunocompromised individuals include *Aspergillus* and *Nocardia* (Moorthy and Rajshekhar, 2008). Brain abscesses from *Nocardia* (Barata *et al*. 2000; Savage *et al*. 1990) and *Cladosporium trichoides* (Silveira *et al*. 2003) have been previously reported in patients on azathioprine. We report the first case of *Salmonella* brain abscess in an immunosuppressed patient from azathioprine.

Both innate as well as adaptive immune mechanisms are important in resisting *Salmonella* infections in humans. Gastric pH, normal intestinal microbial flora, and intestinal lymphoid structures provide innate immunity against the organism following ingestion. The initial stage of infection is

characterized by recruitment of macrophages in response to interferon (INF)-γ that is released by variety of host cells (Mittrucker and Kaufmann, 2000). Although innate immunity may provide an effective restriction of the infection, the organism can overwhelm this system by expressing factors that enhance their pathogenecity and intracellular survival in macrophages (Cirillo *et al*. 1998). Both B cell– and T cell–mediated adaptive responses are important for control of infection (Mittrucker and Kaufmann, 2000; Ugrinovic *et al*. 2003). Our patient had uncontrolled diabetes, had undergone thymectomy, and was on cytotoxic immunosuppressant therapy—factors that impair innate as well as adaptive immune responses. Uncontrolled diabetes impairs innate immunity by decreasing chemotaxis and phagocytic function of the macrophages and polymorphonuclear cells (Geerlings and Hoepelman, 1999). Azathioprine is a prodrug of mercaptopurine that interferes with nucleic acid synthesis, a crucial step in lymphoid cell proliferation in response to antigenic stimulation. Although our patient did not have prior structural brain damage, immunomodulation of myasthenia gravis and presence of uncontrolled diabetes resulted in a dysfunctional immune system that predisposed her to an unusual manifestation of *Salmonella* infection. She had all of the four most commonly reported symptoms and improved following surgical drainage and postoperative antibiotics.

Conclusion

Central nervous system (CNS) infections in adults resulting from *Salmonella* species are extremely uncommon (Cohen *et al*. 1987; Rodriguez *et al*. 1986). Presence of immunocompromised status, as may occur with human immunodeficiency virus (HIV) infection, uncontrolled diabetes, corticosteroids, and immunosuppressive medication, may predispose adults to *Salmonella* bacteremia. Once blood borne, peripheral seeding may result in focal intracranial infections. Based upon our review of *Salmonella* brain abscess cases, the two most important factors predisposing patients to focal intracranial infections are an immunocompromised status and the presence of structural brain damage. The presence of these predisposing factors in a patient with symptoms suggestive of CNS involvement, such as fever, headache, confusion, focal neurological deficits, and seizures, should alert a clinician to this rather unusual presentation of *Salmonella* infection. Tissue cultures are most likely to identify this organism, whereas the sensitivity of blood and stool cultures is low. Surgical excision with prolonged postoperative antibiotics appears to be an appropriate approach to management of these abscesses.

Methods

Articles were searched in MEDLINE (through PubMed, an electronic search engine for published articles, and Ovid), PubMed, and Ovid journals. The terms used for the search were "Salmonella," "focal intracranial infections," "meningitis," "empyema," and "brain abscess." The records containing information on adult population were reviewed. Our analysis focused on identification of immunosuppression, prior structural brain damage, and clinical characteristics of focal intracranial *Salmonella* infections. These results are tabulated in Tables 1 and 2.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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