Diffusion-Weighted MRI Abnormalities in an Outbreak of *Streptococcus agalactiae* Serotype III, Multilocus Sequence Type 283 Meningitis

Kevin Tan, BM BS, MRCP (UK),[1,2]

Limin Wijaya, MBBS (Melb), MRCP (UK), DTMH (UK),[3]

Hui-Jin Chiew, MBBS, MRCP (UK),[1] Yih-Yian Sitoh, MBBS, FRCR (UK),[2,4]

Humaira Shafi, MBBS, Board Cert (IM), Board Cert (ID),[5]

Robert C. Chen, MD, Board Cert (Radiology),[2,6]

Chin Kong Goh, MBBS, FRCR (UK), MMed (Diag Radiol),[7] and

C.C. Tchoyoson Lim, MBBS, FRCR (UK), MMed (Diag Radiol)[2,4]

Purpose: In 2015, an outbreak of group B streptococcal (GBS) infection caused by *Streptococcus agalactiae* Serotype III, multilocus sequence type 283, related to consuming infected raw freshwater fish, affected more than 200 patients in Singapore. We describe the clinical, laboratory, and neuroimaging features of a subgroup of adults with central nervous system (CNS) infections caused by GBS.

Materials and Methods: The database of the Singapore Neurologic Infections Program (SNIP), a national multicenter study for surveillance of infectious neurologic disease, was reviewed to select patients with GBS CNS infection during the outbreak. Cases were diagnosed on the basis of clinical features, cerebrospinal fluid (CSF) findings and identification or isolation of *Streptococcus agalactiae* in the blood or CSF. Demographic, clinical and neuroradiological information was obtained prospectively and retrospectively abstracted.

Results: Fourteen patients (6 male, 8 female; median age, 58 years) presented with fever, meningism, headache, encephalopathy, focal neurological deficits, and/or seizures. All except two were previously healthy. Diffusion-weighted imaging (DWI) on admission was abnormal in 13 patients, showing tiny hyperintensities in the subarachnoid space (7 patients), ventricles (6 patients) and brain parenchyma (8 patients); 5 patients had cerebellar abnormalities.

Conclusion: Among healthy non-pregnant adults infected with Serotype III, multilocus sequence type 283 GBS meningitis linked to eating infected raw freshwater fish, DWI detected small pus collections and unusual cerebellar involvement. A collaborative national surveillance system that includes MRI can be helpful during unusual food-borne zoonotic infectious disease outbreaks.

Level of Evidence: 4

Infectious neurologic disease such as meningitis and encephalitis are a tremendous public health problem world-wide and often cause devastating sequelae.[1] Recent fatal outbreaks of central nervous system (CNS) infection including West Nile virus in North America,[2] Nipah virus in Malaysia and Singapore,[3,4] and bat lyssaviruses in the

United Kingdom[5] have caused public health concerns, and highlighted the dangers of zoonotic transmissions of novel or emerging organisms across the species barrier, as well as drawn attention to the need for vigilance and public health surveillance. Unfortunately, due to its low incidence and logistical challenges in multidisciplinary collaboration, CNS infection is difficult to study prospectively, and MRI characteristics of infectious diseases are not well-described. The Singapore Neurologic Infections Program (SNIP) was set up as a prospective multi-hospital, multidisciplinary, nationwide surveillance study to capture, describe and study the epidemiology of CNS infections and to identify and assist in outbreak detection in Singapore.[6]

Since December 2014, an unusual cluster of patients with group B streptococcus (GBS) infection amongst healthy nonpregnant adults was observed in Singapore. The cause of the outbreak, thought to be related to consuming infected raw freshwater fish, is currently being investigated.[7,8] GBS is a common gastrointestinal and genitourinary commensal organism, and although it is an important cause of bacteremia and meningitis in neonates and pregnant women, it seldom causes disease in healthy adults; food-borne zoonotic GBS infection has not been well-described in the literature.[9] Although there is recent recognition that this organism is a cause of substantial morbidity and mortality among patients with chronic underlying conditions, such as diabetes mellitus, malignancy, neurologic disorders, and skin diseases,[10–12] these adults with invasive GBS infection and comorbidities typically suffered from urinary tract and soft tissue infection, osteomyelitis, infective endocarditis and pneumonia; only a minority had meningitis.[13–19] During the Singapore outbreak of GBS infection, an increased frequency and unusual manifestations were noticed during the prospective surveillance of acute CNS infections by the SNIP investigators and other physicians (T. Barkham and B. Ang, unpublished data). We describe here the clinical, laboratory, and neuroimaging features of a cluster of adults with CNS infections caused by GBS.

Materials and Methods

Patient Identification
As part of the SNIP protocol, patients with meningoencephalitis were prospectively enrolled from infectious diseases, neurology and pediatric services, and intensive care units in five public general hospitals and the National Neuroscience Institute. A patient with meningoencephalitis was defined as one aged >1 month who was hospitalized with (1) an acute onset of illness clinically suspicious for CNS infection, or (2) at least 2 of the following (a) fever or history of fever (≥38°C) during the presenting illness, (b) new onset seizures, (c) focal neurological deficits, (d) depressed or altered level of consciousness, (e) cerebrospinal fluid (CSF) pleocytosis (> 4 cells/μL), (f) abnormal neuroimaging suggestive of CNS infection, or (g) abnormal electroencephalogram (EEG) suggestive of CNS infection. This study was approved by the SingHealth Centralised Institutional Review Board (Ref 2013/374/F) and National Healthcare Group Domain Specific Review Board (Ref 2013/01259).

Cases of GBS meningitis were diagnosed on the basis of clinical features of acute meningitis, CSF abnormalities, identification or isolation of GBS in the blood or CSF. A primary distant focus of infection was considered when a patient had clinical symptoms and signs that were consistent with focal infection distant from the CNS, and GBS was isolated from the primary focus or from blood culture.

Data Collection
Clinical and epidemiologic data were obtained from patients and/ or their family by interview and assessed prospectively by the investigators. Demographic and laboratory data from the clinical notes were also obtained at the point of enrolment.

Neuroimaging
We reviewed MRI studies of patients on admission to hospital; all MRI studies were conducted on either 1.5 Tesla (T) or 3.0T clinical scanners. Pulse sequences performed included at least diffusion-weighted imaging (DWI) (repetition time/echo time, 2600–8200/60–100, single-shot spin-echo echo planar imaging, $b = 1000$ s/m^2), fast spin-echo T2-weighted imaging (3000-5600/85–100 effective) or FLAIR (7000–11 000/85–135; inversion time, 2200-2800 ms). Gradient-recalled echo (680-860/15-25; 15-20 degree flip angle) or susceptibility weighted imaging (27-49/20–40, 15 degree flip angle), various contrast-enhanced sequences after 0.1 mmol/kg body weight of intravenous gadolinium chelate contrast media), and time-of-flight MRA (20–33/2.7–7.0, 15-25 degree flip angle, 0.6 mm thickness) of the intracranial circulation was also performed in some patients. All images were 5-mm-thick with a spacing of 1 mm. All images were analyzed independently by two radiologists (C.C.T.L., Y.Y.S., with 21 and 22 years of specialist experience, respectively) who were not blinded to clinical information. The location, number and maximum diameter of intracranial abnormalities was recorded; lesions measuring < 7 mm were described as tiny.

Results

Clinical
Fourteen patients with GBS CNS infection were identified. The median age at disease onset was 58 years (range, 22 to 81 years); 6 patients were male, 8 female. Presenting symptoms were fever (14 of 14; 100%), meningism (8 of 14; 57%), headache (7 of 14; 50%), encephalopathy (6 of 14; 43%), focal neurological deficits (5 of 14; 36%), and/or seizures (2 of 14; 14%). Comorbidities include two with diabetes mellitus (one patient had previous breast carcinoma on treatment with letrozole), one each with childhood epilepsy and previous meningoencephalitis. All patients were community dwelling; none were hospital inpatients or residents of long-term facilities. Three patients were subsequently admitted to the intensive care or high dependency units; 1 required intubation.

Three patients presenting with focal neurological deficits had sudden onset of symptoms and were initially

TABLE 1. MRI Findings on Admission in 14 Patients with Group B Streptococcus Meningoencephalitis[a]

Case no./ age (yr)/ sex	Hospital day of MR examination	Number: location of DWI hyperintensity in subarachnoid space & ventricles	Number: size, location of brain DWI hyperintensity	T2/FLAIR hyperintensity	Contrast enhancement	MRA	Other MRI changes
1/81/F	1	None	None	Normal	NP	Normal	Old lacunar infarcts, deep microhemorrhages
2/22/M	9	1: Lt paramedian frontal sulcus	None	Not visible	Normal	NP	No
3/57/F	5	1: Lt lateral ventricle	None	Not visible	Normal	Normal	Incidental gray matter heterotopia
4/74/M	4	5: Lt paramedian frontal sulcus, bil Sylvian fissures, bil lateral ventricle	None	Not visible	Mild diffuse meningeal	NP	Old lacunar infarcts, periventricular leukoariosis
5/63/M	3	2: Rt lateral frontal sulcus, Lt lateral ventricle	None	Not visible	Mild diffuse meningeal	NP	Deep microhemorrhages
6/55/M	6	5: Rt paramedian frontal sulcus, Rt medial parietal sulcus, bil lateral ventricles	1: tiny Lt corona radiata	Tiny Lt corona radiata	Mild diffuse meningeal	NP	No
7/61/F	2	None	1: 30mm Rt frontal cortex & white matter	Not visible	NP	Normal	No
8/50/F	4	2: Lt lateral frontal sulcus, Lt lateral ventricle	1: 31mm cerebellar vermis	31mm cerebellar vermis	Mild diffuse meningeal	Lt MCA narrowing	No
9/59/F	10	2: bil lateral ventricles	8: 29mm cerebellar vermis, tiny bil cerebellar hemispheres, tiny midbrain, tiny Lt thalamus	Not visible	Mild diffuse meningeal	Normal	Tiny microhemorrhage within abnormal cerebellar vermis

TABLE 1: Continued

Case no./ age (yr)/ sex	Hospital day of MR examination	Number: location of DWI hyperintensity in subarachnoid space & ventricles	Number: size, location of brain DWI hyperintensity	T2/FLAIR hyperintensity	Contrast enhancement	MRA	Other MRI changes
10/55/M	5	>20: bil medial & lateral frontal & lateral temporal sulci	9: 42mm cerebellar vermis, 14mm & 12mm Rt cerebellar hemisphere, 20mm Lt PLIC, tiny Lt cerebellar hemisphere, tiny Rt midbrain	Not visible	Mild diffuse meningeal	Bil PCA, Lt ACA narrowing	Deep microhemorrhages
11/59/F	4	None	3: 22mm Lt cerebellar hemisphere, tiny Rt basal ganglion, tiny anterior corpus callosum	22mm Lt cerebellar hemisphere	NP	NP	Old lacunar infarcts, deep microhemorrhages
12/66/F	5	None	5: 45mm Rt frontal cortex & white matter, 39mm Lt frontal cortex & white matter, 22mm cerebellar vermis, tiny Rt basal ganglia, tiny Lt cerebral peduncle	Same	NP	Normal	Old lacunar infarcts
13/24/M	2	7: Lt lateral & medial parietal/ frontal sulci	None	1: 63mm Lt frontal cortex & White Matter	Mild diffuse meningeal	Lt MCA narrowing	No
14/32/F	9	None	1: Tiny cerebellar vermis	4: 20mm cerebellar vermis, bil entire basal ganglia, genu corpus callosum	Mild diffuse meningeal, focal cerebellar enhancement	Normal	No

[a]DWI = diffusion-weighted imaging; MRA = MR angiogram; FLAIR = fluid-attenuated inversion recovery; Rt = right; Lt = left; bil = bilateral; PLIC = posterior limb of the internal capsule; NP = nor performed; MCA = middle cerebral artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery.
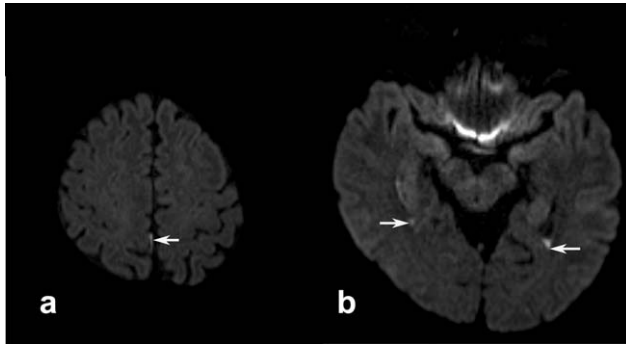
FIGURE 1: Case 6 GBS meningitis. Tiny discrete focal hyperintense abnormalities (arrows) are seen only on DWI in the posterior right interhemispheric fissure (a) and lateral ventricles (b).

diagnosed as stroke (cases 7, 10, and 13); eight were diagnosed clinically with meningoencephalitis (cases 1–5, 8, 12, and 14). Four patients had joint pain and/or swelling: case 6 (right little finger and left knee), case 9 (back), case 10 (right shoulder, neck and lower back), and case 11 (right knee swelling).

Laboratory
GBS was detected in 13 of 14 blood cultures, and 8 of 11 CSF cultures; one patient had GBS detected on CSF 16S ribosomal RNA sequencing. GBS culture was positive in urine from case 10 and right knee aspiration from case 11.

Neuroimaging
All patients underwent MRI brain scans within 2 weeks (range: 1–10 days) of symptom onset. Neuroimaging data on admission for each case are summarized in Table 1.

On initial MRI, 13 studies were abnormal; 1 was normal. In all abnormal MRI studies, DWI showed two patterns of focal abnormalities of increased signal intensity: (a) within the subarachnoid space and ventricles, and (b) within the brain parenchyma.

Nine patients had single or multiple tiny focal abnormalities involving the subarachnoid space (seven patients) and ventricles (six patients) (Figs. 1 and 2a). In eight patients, DWI hyperintensities were detected involving the brain parenchyma (Fig. 2b). These abnormalities ranged from tiny hyperintensities in the basal ganglia, corona radiata, thalamus, midbrain, cerebral peduncle, and corpus callosum, to larger lesions 20–45 mm in the posterior limb of the internal capsule, frontal and parietal cortex, and white matter. The cerebellum was affected in five patients, with DWI hyperintensities ranging from tiny hemispheric lesions, to larger lesions measuring 42 mm in the vermis (Fig. 2c). Reduced ADC was seen in the larger DWI hyperintense lesions (Fig. 2d), but in the tiny lesions, ADC could not be reliably measured.

On conventional T2-weighted or FLAIR images, only some of the larger lesions were detected; the tiny ventricular, subarachnoid, and brain parenchymal DWI hyperintense lesions were not visible. In cases 13 and 14, additional hyperintense lesions were detected on T2-weighted or FLAIR images that were not visualized on DWI. Case 13 had multiple tiny subarachnoid focal hyperintensities on DWI, but the adjacent left parietofrontal cortex and white matter showed high signal intensity only on T2-weighted images, not on DWI. In case 14, the cerebellar vermis lesion
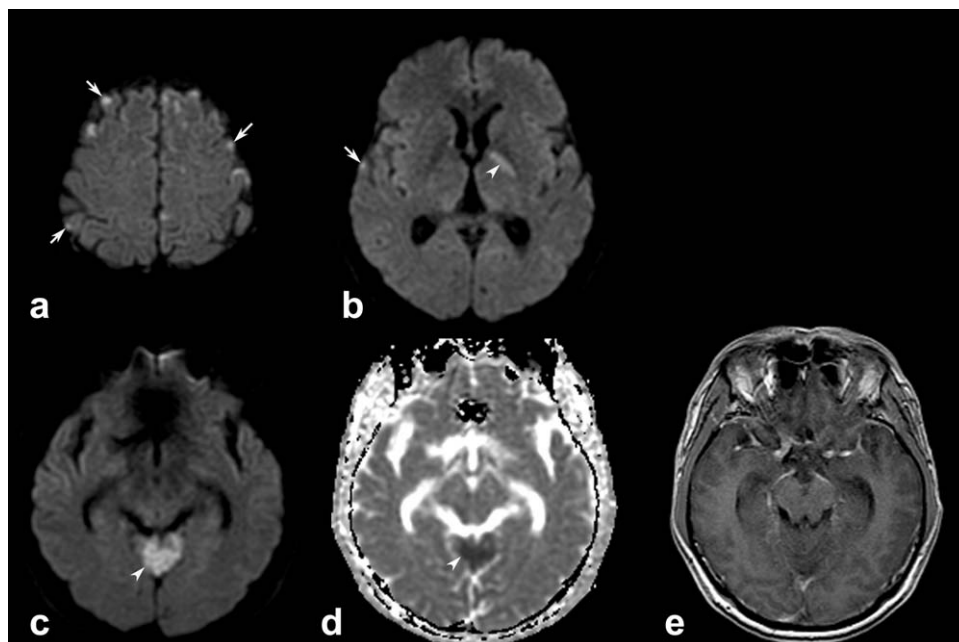
FIGURE 2: Case 10 GBS meningitis. Multiple tiny hyperintensities are seen in the subarachnoid space in the left temporal and bilateral frontal regions (a, arrows) on DWI. Larger abnormalities are seen in the posterior limb internal capsule (b) and cerebellar vermis (c, arrowheads), with reduced ADC (d, arrowhead). The cerebellar lesion is not visible on conventional contrast-enhanced MRI (e).
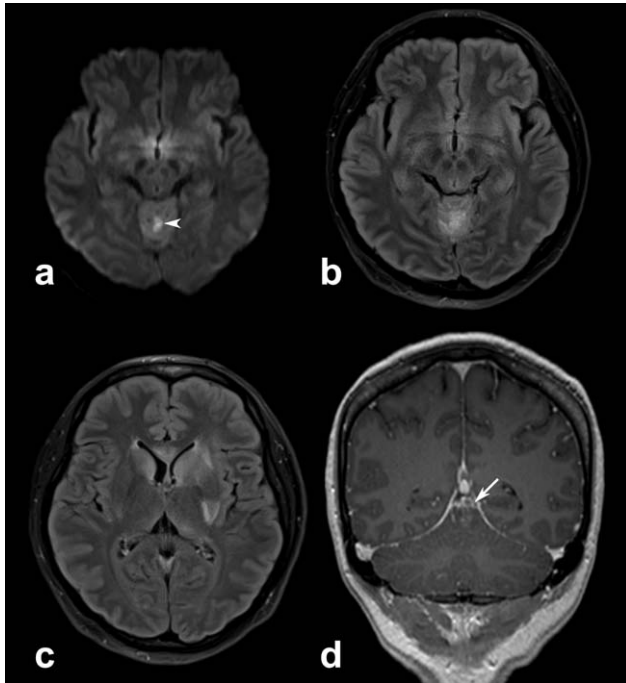
FIGURE 3: Case 14 GBS meningitis. A tiny hyperintensity is detected on DWI in the cerebellar vermis (a, arrowhead) and on FLAIR image (b). FLAIR images also detected additional abnormalities in the basal ganglia bilaterally and the adjacent genu of the corpus callosum (c), which were not seen on DWI. Focal moderate cerebellar enhancement on a background of mild generalized enhancement was noted after contrast injection (d, arrow).

was more extensive on T2-weighted and FLAIR images than on DWI (Figs. 3a,b), and there were additional abnormalities in the basal ganglia bilaterally and the adjacent genu of the corpus callosum (Fig. 3c).

Ten patients underwent contrast-enhanced studies; 2 studies did not show abnormal enhancement, 8 had mild generalized leptomeningeal enhancement (Fig. 2e). In case 14, focal moderate cerebellar enhancement on a background of mild generalized enhancement was noted (Fig. 3d). MR angiography was performed in eight patients: five were normal; three studies showed focal irregularity or narrowing in the middle cerebral arteries, posterior cerebral arteries, and anterior cerebral arteries. Other abnormalities, thought to be unrelated to the current episode, were detected in seven patients, ranging from old lacunar infarcts, microhemorrhages, and incidental heterotopic gray matter.

Other Investigations

All patients had transthoracic echocardiography, which were negative for infective endocarditis. Two patients (cases 11 and 12) went on to have transesophageal echocardiography: case 11 had mitral valve vegetation.

Discussion

SNIP surveillance identified a cluster of 14 adult patients admitted to hospital with CNS infection related to a wider outbreak of food-borne GBS infection. In this study, we described some unusual clinicoradiological features. Typically, GBS affects neonates, and invasive GBS infection is rare in healthy adults.[9] Before December 2014, the incidence of non-neonatal GBS infections in Singapore was low at an average of 2.9 cases per week. However, from January to June 2015, there were 238 cases of GBS infections, and the outbreak and its link to consumption of raw freshwater fish, came to light in July 2015.[7,8] The patients in our cohort were all healthy, community-dwelling adults, and only a few had diabetes mellitus, recent malignancy or neurologic disorders, which are recognized risk factors for developing invasive GBS disease.[10–12] Most of our patients presented with fever, headache, meningism, or encephalopathy, classical features of meningoencephalitis, but a few had a stroke-like presentation. In addition to GBS infection of the CNS, some of our patients also had more widespread infections including arthritis and endocarditis.

In the recent past, clusters of patients with unusual CNS manifestations and abnormal DWI and computed tomography have been described in infectious disease outbreaks in Singapore. These included detecting microinfarction in Nipah virus encephalitis from a novel pig-borne virus[3,20,21] and large artery thrombosis in severe acute respiratory syndrome or severe acute respiratory syndrome, a novel zoonotic coronavirus causing pneumonia.[22] These early case descriptions based on multi-hospital and multidisciplinary collaborations in situations of important public health hazards, enabled local investigators to conduct surveillance and follow-up of patients. Our current study thus illustrates the potential contribution of MRI in surveillance programs such as SNIP to identify and report unusual patterns of cases of CNS infection.[20–22]

In our cohort of patients, initial MRI detected conspicuous abnormalities on DWI, consistent with meningitis and pus in the subarachnoid space and lateral ventricles caused by GBS meningitis. Meningeal infection due to bacteria, tuberculosis or fungi can cause subarachnoid DWI hyperintensities in both adult and children, in addition to conventional MRI features such as meningeal enhancement, cerebral abscess formation, or hydrocephalus.[23–26] Furthermore, sulcal and ventricular DWI abnormalities have been described to occur more often in *Streptococcus pneumoniae*, compared with meningitis caused by other organisms, and our cases, caused by *Streptococcus agalactiae*, appear to show similarities.[24] In some of our patients, these tiny abnormalities in the dependent portions of the occipital horns were the only abnormal finding in an otherwise normal MRI study, consistent with past reports that DWI was more conspicuous and sensitive to detection of ventricular pus than conventional pulse sequences.[27,28] Unlike GBS that affects neonates by means of maternal transmission, there are few reports of MRI findings in adult GBS, but features similar

to ours have also been described.[26] Our results highlight the utility of DWI to detect and diagnose subtle findings in CNS infection.[28,29]

In many patients, we also found DWI hyperintensities in the brain parenchyma suggestive of cerebral infarction. These lesions were hyperintense on early DWI (within 10 days of symptom onset), many were not visible on conventional T2-weighted or FLAIR images, and all did not enhance after contrast injection. These features are suspicious of acute focal or multifocal subcortical cerebral infarction[30] which can complicate bacterial meningitis[31–34] and viral encephalitis.[20,21,35] However, the pattern of our DWI findings differed from the large territorial cerebral infarction and vasculitic narrowing of the major intracranial arteries detected on MR angiography previously described in neonatal GBS.[17–19,23] The relationship between CNS infections and acute ischemic stroke is complex,[33,34] and alternative explanations for MRI findings other than cerebral infarction, including cerebritis from direct infection by bacterial invasion, also need to be considered.[24,36]

The cerebellar MRI findings in our patients are also unusual for CNS infection: they did not correlate with clinical features and are difficult to characterize. The cerebellum may be involved in CNS infection, either by direct invasion (typically described in Listeria monocytogenes, Mycoplasma pneumonia, typhoid fever, Lyme disease, and Whipple disease) or later in the course of disease from post-infectious immune-mediated mechanisms, with several small neuroimaging series describing normal MRI or diffuse cerebellar swelling with hydrocephalus and brain herniation.[37,38] However, the distinction between direct invasion and immune-mediated damage is difficult, and neither finding has been well-described in GBS infection. On the other hand, the findings on DWI in our patients bear some similarity to the typical multifocal and patchy appearance of acute cerebellar infarction.[39] Hence, we postulate that at least some of the findings in our patients with small, multifocal involvement of the gray matter of the vermis and hemispheres may be more consistent with cerebral infarction rather than direct infectious cerebellitis. Other, more complex MRI features such as case 14 with T2-weighted rather than DWI involvement of the entire basal ganglia, are unexplained, and the unifying pathological cause for the DWI hyperintensities still remains to be elucidated.

Our study is preliminary and has many limitations. As it reports only the initial MRI findings on admission in patients enrolled in SNIP in an ongoing infectious outbreak, comparison with a nationally co-ordinated database of cases (S. Kalimuddin, unpublished data) affecting the CNS, heart, and joints would be useful. GBS infection can be classified according to serotypes (I to IX), and initial studies suggest that this outbreak associated with consumption of raw freshwater Song fish (bighead carp) and Toman fish (snakehead),

was associated with *Streptococcus agalactiae* serotype III, specifically sequence type (ST) 283.[40] This potential foodborne zoonotic source had previously been reported to cause severe disease in farmed fish in Asia, and further study is needed to determine virulence factors of the bacteria which could account for the severity and relative incidence of complications, as well as the pathological features and source of the outbreak.[7,8,41,42] Because meningitis and cerebral infarction have been previously reported to be associated with poor prognosis, follow-up studies of our patients will also be needed, as would comparison of MRI features of meningitis caused by GBS and other organisms.[26] Nevertheless, our initial findings demonstrate that some patterns of MRI features that may be useful to alert clinicians and radiologists to the novel GBS CNS infection outbreak involving *Streptococcus agalactiae* Serotype III.

In conclusion, among adults with GBS meningitis linked to consuming raw freshwater fish, DWI detected small subarachnoid, ventricular, and brain lesions, including unusual cerebellar involvement. A collaborative national surveillance system can be helpful for detecting outbreaks of unusual or emerging food-borne zoonotic CNS infection in Singapore.

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