Late-Onset Group B Streptococcal Meningitis Has Cerebrovascular Complications

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Objective To describe cerebrovascular diseases related to late-onset group B *Streptococcus* (GBS) meningitis.

Study design Retrospective case series. Patients treated for cerebrovascular complication of late-onset GBS meningitis over 5 years were identified through neuroradiology and microbiology databases. Patient charts were reviewed with regard to clinical presentation, laboratory findings, including GBS subtype, treatment, clinical course, and outcome. Cerebral magnetic resonance imaging was reviewed with special emphasis on stroke pattern and cerebrovascular findings.

Results Fourteen patients were identified. In 6 out of 9 patients serotype III was causative and positive for surface protein hvgA in 5. Ten had arterial ischemic stroke accompanied by a cerebral sinovenous thrombosis in 2 patients. Evidence of cerebral vasculopathy was found in 4 cases. The stroke pattern was variable with cortical, multifocal ischemia, basal ganglia involvement, or had a clear territorial arterial infarction. Ten patients were treated with anticoagulation. No significant bleeding complications, and no recurrent strokes occurred. Twelve patients had clinical and/or subclinical seizures. Developmental outcome was good in 8 cases. Six patients had moderate to severe developmental delay. Central nervous system complications included subdural empyema, hydrocephalus, epilepsy, microcephaly, and hemiplegia.

Conclusions Late-onset GBS meningitis can be complicated by severe cerebrovascular disease, including arterial ischemic stroke and cerebral sinovenous thrombosis. These complications may be underestimated. We recommend a low threshold for cerebral imaging in these cases. Future studies on the exact incidence, the role of GBS subtypes, and on safety and efficiency of preventive anticoagulation therapy are warranted. *(J Pediatr 2015;166:1187-92)*.

The incidence of arterial ischemic stroke in childhood is highest in the first year of life, even with the exclusion of neonates.[1] Presumably, this is a result of differences between underlying age-related risk factors. In infancy, infection likely plays a more prominent role in arterial ischemic stroke.

Group B *Streptococcus* (GBS, also known as *Streptococcus agalactiae*) infections are a leading cause of neonatal morbidity and mortality. These infections can manifest early (ie, from birth to day 6 of life) (early-onset disease [EOD]) or later (ie, from day 7 of life to 3 months of age) (late-onset disease [LOD]). Infants with GBS infections after the first week of life commonly have bacteremia and more frequently develop meningitis than do those with EOD.[2] Recent data from England and Wales suggest that there is an increase in the incidence of bacterial meningitis in children <3 months of age, with GBS being one of the leading causes.[3] Whereas maternal screening programs accompanied by intrapartum antibiotic prophylaxis have resulted in a decrease in early-onset GBS disease, the incidence in late onset GBS meningitis appears to be stable or even increasing.[2-5]

Perinatal stroke has been reported as a complication of neonatal GBS meningitis and sepsis.[6,7] Little is known about strokes related to late-onset GBS infection.

Methods

Fourteen patients from 3 institutions (The Hospital for Sick Children [HSC], Toronto, Canada; Leverkusen Children's Hospital, Germany; University Children's Hospital, Dusseldorf, Germany)

CPS	Capsular polysaccharide
CSF	Cerebrospinal fluid
CSVT	Cerebral sinovenous thrombosis
EOD	Early-onset disease
GBS	Group B *Streptococcus*
HSC	Hospital for Sick Children
LOD	Late-onset disease
MCA	Middle cerebral artery
MR	Magnetic resonance
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction

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with cerebrovascular complications of late-onset GBS meningitis are included in this study. All patients presented acutely during a 5-year period (2009-2014). Twelve of the 14 patients were treated at the HSC, Toronto, Canada. The remaining 2 patients were seen by one of the authors (D.T.) at the 2 other institutions. Inclusion criteria of the study were: (1) older than 7 days of age (LOD), younger than 4 months; (2) GBS meningitis, defined as having both clinical evidence of central nervous system infection on history and physical examination as well as the following laboratory findings: (a) GBS-positive cerebrospinal fluid (CSF) or blood culture, or positive latex agglutination test result on CSF sample; or (b) CSF analysis consistent with bacterial meningitis (protein level >0.40 g/L, low glucose <2.1 mmol/L, and leukocytosis); (3) acute brain magnetic resonance imaging (MRI) performed (day 1-14 after symptom onset), including diffusion weighted imaging and apparent diffusion coefficient; and (4) brain MRI evidence of cerebral infarction (diffusion weighted imaging and apparent diffusion coefficient or T2) and/or evidence of significant vasculopathy or cerebral sinovenous thrombosis (CSVT) on magnetic resonance (MR) angiography or venography (time-of-flight). MRI findings were reviewed independently by 2 pediatric neurologists (D.T., R.A.).

All medical records were reviewed with respect to age, sex, clinical presentation, maternal GBS status, blood and CSF testing results, treatment, and complications. Neurologic outcome was documented based on the most recent follow-up visit. Patients who were evaluated at the stroke clinic for follow-up visits were seen by at least 1 child neurologist with special expertise in the field of childhood stroke (D.T., A.S., R.A.). Follow-up examination included a complete internal and neurologic examination, including developmental screening. Three patients were seen in neurosurgery clinic only (case 8), neurosurgery and thrombosis clinic (case 14), or neonatal follow-up clinic (case 12). Outcome was either classified as "normal" when no deficit was found or "abnormal" when focal neurologic abnormalities or developmental delay were identified.

Microbiology Data

Organisms isolated from blood or CSF were confirmed to be *Streptococcus agalactiae* (GBS) by conventional methods (ie, beta hemolysis, Gram stain appearance, catalase production, Lancefield antigen grouping, and hippurate hydrolysis). Polymerase chain reaction (PCR) amplification of a 234-bp region of the monocopy regulatory gene *dltR*, which is specific to GBS was used to confirm *S agalactiae* species identification. Primers and amplification conditions were those previously described.[8]

In 9 patients (all from the HSC), GBS capsular typing was performed. Serologic determination of the capsular polysaccharide (CPS) types was performed by latex agglutination (SSI Diagnostica; Statens Serum Institute, Copenhagen, Denmark) as previously described.[9] CPS types were also determined by PCR amplification of CPS type-specific regions of the *cps* locus. PCR conditions were as described,[10,11] with the exception that we used KOD Hot Start DNA Polymerase (EMD Millipore, Billerica, Massachusetts). Primers ST-17S and ST-17AS were used as described previously to amplify the S10 domain of the surface protein HvgA, which is unique to GBS strains of multilocus sequence typing clonal-complex-17.[8]

Prothrombotic Evaluation

As part of routine evaluation, patients suffering a stroke who were followed in stroke or thrombosis specialty clinic were tested for prothrombotic conditions. Evaluation included lipoprotein A, activated protein C resistance, antiphospholipid screen, antithrombin, fibrinogen, factor IX, VIII, XI, homocysteine, protein C, protein S free antigen, factor V Leiden, and prothrombin gene.

Anticoagulation Treatment Protocol

Anticoagulation treatment followed the HSC guidelines. According to these guidelines, unfractionated heparin maintenance dose (no bolus) was 28 units/kg/h intravenous for patients ≤1 year of age. Unfractionated heparin dose was adjusted to maintain heparin anti-factor Xa level between 0.35-0.7 units/mL. Low molecular weighted heparin, Enoxaparin dose was 1.5 mg/kg/dose subcutaneous q12h for patients ≤2 months of age or 1 mg/kg/dose subcutaneous q12h for patients >2 months of age.

Results

Fourteen patients were identified. Demographics and clinical data for each case are summarized in **Table I** (available at www.jpeds.com). Nine patients were male, 5 female. The age at onset ranged from 8 days to 3 months. The maternal GBS status was negative in 9, positive in 2, and unknown in 3. All but 2 patients were born at term and had an uncomplicated perinatal courses. Two patients were preterm babies (case 8 and 12), born at 25 and 30 weeks. No central nervous system complications had occurred in the neonatal period and prior cranial ultrasonography did not reveal any parenchymal lesion. Presenting symptoms were nonspecific (reduced drinking, lethargy, irritability, fever, breathing abnormalities). All patients were admitted to the intensive care unit, 10 required intubation and 7 of these were treated with inotropic drugs. In 8 patients focal seizures were seen during the first 24 hours after symptom onset. In 7 of 9 patients monitored with continuous electroencephalogram, subclinical seizures were documented. Clinical and subclinical seizures were treated with anti-epileptic medications. All patients were treated with appropriate antibiotics (**Table II**). GBS cultures were positive in CSF (n = 2), blood (n = 2), or both (n = 9). Latex agglutination on CSF was positive in one (**Table II**). In cases 4 and 5, no positive CSF culture result was available. Case 4 had lumbar puncture performed while receiving antibiotic treatment, but had significant pleocytosis and GBS positive blood culture. Case 5 did not have CSF examined; the diagnosis of meningitis was based on clinical, laboratory,

Table II. Microbiology data and antibiotic treatment

Case number	GBS positive specimen	Serotype	ST-17 PCR	Antibiotics before GBS detection	Antibiotics after GBS detection
1	CSF/blood	n/a	n/a	Vancomycin, cefotaxime, gentamicin, ampicillin	Penicillin G
2	CSF/blood	n/a	n/a	Aciclovir, cefotaxime, gentamicin	Penicillin G
3	CSF	n/a	n/a	Aciclovir, cefotaxime, gentamicin	Penicillin G
4	Blood	III	–	Vancomycin, ceftriaxone, penicillin G	Penicillin G
5	Blood	III	+	Vancomycin, ceftriaxone	Penicillin G, Gentamicin
6	CSF/blood	III	+	Ampicillin, gentamicin	Penicillin G
7	CSF/blood	Ib	–	Vancomycin, ceftriaxone, acyclovir	Penicillin G
8	CSF	III	+	Vancomycin, cefotaxime, acyclovir	Penicillin G
9	CSF/blood	III	+	Vancomycin, ampicillin, cefotaxime	Penicillin G
10	CSF/blood	III	+	Vancomycin, cefotaxime, gentamicin, acyclovir	Penicillin G, Gentamicin
11	CSF/blood	Ia	–	Ampicillin, cefotaxime	Penicillin G
12	CSF/blood	Ia	–	Vancomycin, gentamicin	Penicillin G
13	CSF/blood	n/a	n/a	Vancomycin, cefotaxime	Penicillin G, Gentamicin, cephalexin
14	CSF latex agglutination	n/a	n/a	Vancomycin, cefotaxime, acyclovir	Ceftriaxon

n/a, not available.

and imaging findings (nuchal rigidity, shock, positive blood culture, MRI showing ischemia, and empyema).

In 6 of the 9 patients for which GBS serotyping was available, serotype III was identified. Five of these were *hvgA* positive (83%; Table II). Serotype Ia was identified in 2 and Ib in 1 patient, all of which were *hvgA* negative (Table II).

MRI showed evidence for acute (n = 11) or subacute ischemic infarction (n = 2) in all but 1 patient who had an isolated, severe vasculopathy without a stroke (Figure, A and B). Cases 3 and 13 had a CSVT in addition to the arterial ischemic stroke. The remaining 11 patients had arterial ischemic strokes with (4 of 11; Figure, E and G) or without cerebral vasculopathy (7 of 11). The stroke location was variable, predominantly cortical (Figure, C, H, and I) with bilateral involvement. Coexistence of a cortical pattern with basal ganglia involvement also was observed (Figure, C). A clear territorial arterial infarction was seen in patients 2, 6, 8, and 10 (Figure, D-F, and H). Neuroimaging findings of all cases are summarized in Table III.

Ten patients (71%) were treated with anticoagulation (IV heparin or low molecular weight heparin) according to aforementioned guidelines. Indications for anticoagulation were: secondary stroke prevention in 7 of 10, vascular line-related clots in 2 of 10, and primary stroke prevention in 1 of 10 (Table III). None of the patients treated with anticoagulation therapy had clinically significant bleeding complications. However, in patients 10 and 14 a small area of hemorrhage within the infarcted zone led to discontinuation of heparin after 2 days.

Evaluation for thrombophilia was performed in 10 patients and was normal in 9. One patient (case 5) had elevated lipoprotein A (77 mg/dL). No patient had disseminated intravascular coagulopathy.

The mean time of follow-up was 17 months (6-48 months). Developmental outcome at the most recent examination by the treating neurologist revealed normal development in 8 of 14 patients and focal neurologic deficits and/or developmental delay in 6 patients (Table I). There was no stroke recurrence.

Discussion

We describe the presentation, management, and outcome of a cohort of patients with cerebrovascular disease in the context of late-onset GBS meningitis. Fourteen patients were identified within a 5-year period, among these 12 from a single institution (HSC). The fact that 8 of these 12 cases were observed within a 2-year time frame has led us to speculate that strokes may be an under-reported complication of GBS meningitis. With the increasing availability of MRI in tertiary pediatric centers, a lower threshold to perform a cerebral MRI in cases with LOD is possible. Future population-based studies will be helpful in elucidating the exact incidence of strokes complicating LOD.

Our cases of GBS-associated cerebrovascular complications included 1 case of isolated basilar vasculopathy without evidence of cerebral ischemia and 13 patients with ischemic strokes, accompanied by a cerebral sinus venous thrombosis in 2 cases. Two different patterns of ischemic injury were found. The majority of our cases had multiple bilateral, mainly cortical lesions consistent with a diffuse process of injury such as cerebritis and secondary vasculitis involving large and small vessels. The ischemic lesion was located in a clearly defined arterial territory in 4 cases. Four of the neonates and infants with stroke had additional evidence of a vasculopathy on computed tomography or MR angiography as evidenced by large vessel stenosis and/or beading appearances of multiple large and medium size vessels.

Few reports on cerebral infarction in the context of GBS meningitis have been published, mostly describing strokes in neonates, including 4 with LOD.[5] One additional published case of LOD-related stroke[12] had bilateral focal cerebral infarctions in the penetrating branches of the middle cerebral artery (MCA), widespread stenosis of both internal carotid artery and basilar arteries, and a CSVT thrombosis of the straight sinus.

In general, cerebrovascular complications of bacterial meningitis are well known. In 1981, the incidence of cerebral infarction was described to be as high as 30% in a study of

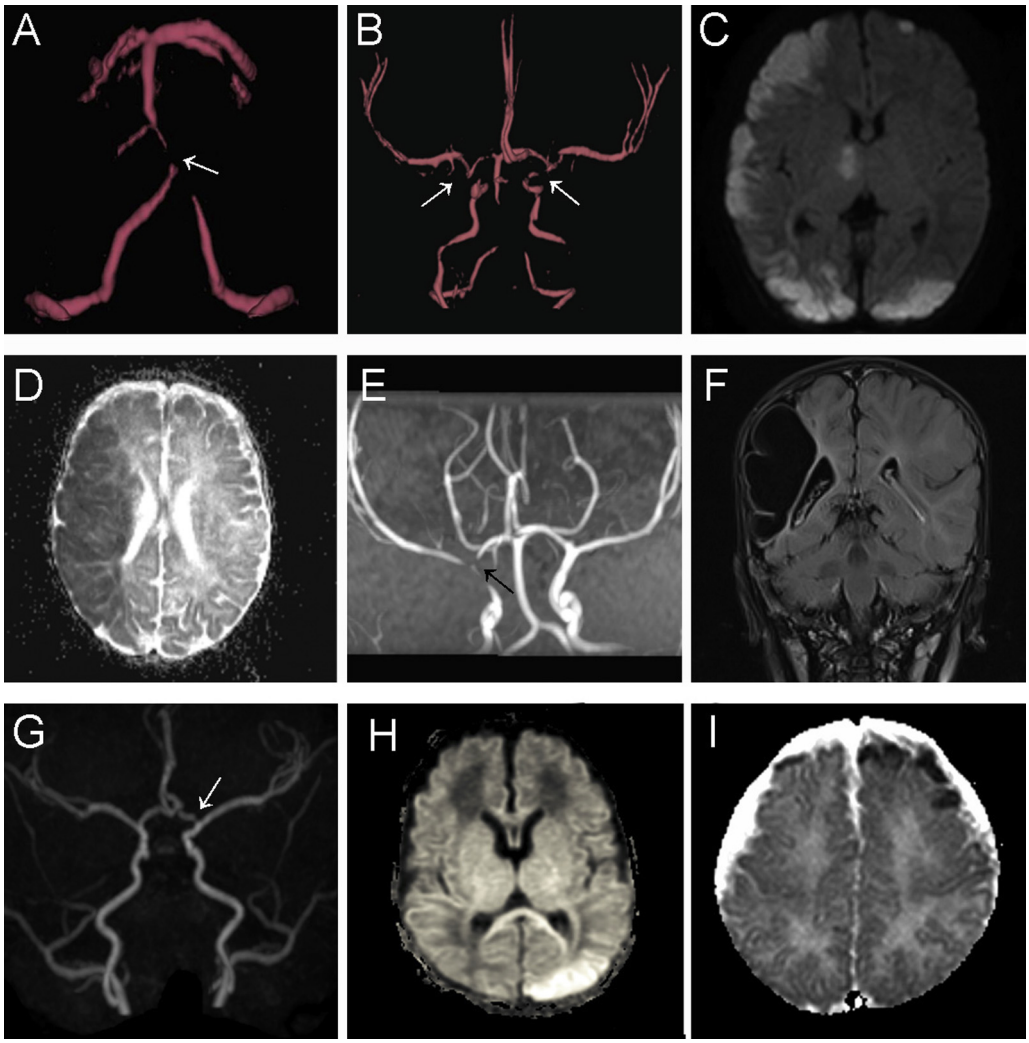

Figure. Examples of neuroimaging findings found in the study cases. **A** and **B,** On the 3-dimensional time of flight MR angiography severe stenosis of the **A,** basilar artery (*arrows*) and **B,** both terminal internal carotid arteries can be seen (*arrows*). **C,** Multifocal superficial cortical infarction with diffusion restriction on the diffusion weighted images. In addition, there is ischemic infarction involving the right thalamus. **D,** Apparent diffusion coefficient maps showing an acute ischemic lesion involving the complete MCA stroke territory. **E** and **F,** MR angiography reveals a severe stenosis and reduced flow within the right distal internal carotid artery and the proximal MCA (*arrow*) of the same patient. **F,** On follow-up 3 months later MRI shows encephalomalacia in the former stroke area. **G,** MR angiography reveals a stenosis of the A1 segment of the anterior cerebral artery. **H,** Ischemic infarct involving left posterior, inferior temporal, and occipital lobe. Additional involvement of the splenium of the corpus callosum. **I,** Left more than right frontal, superficial infarction (apparent diffusion coefficient maps).

childhood bacterial meningitis using computed tomography.[13] *Streptococcus pneumoniae* was the most frequent causative pathogen. A recent population-based study from the United Kingdom found evidence for cerebrovascular disease in 10 of 24 children with pneumococcal meningitis.[14]

Although we did not have a complete sample of the isolates from infants infected in this series, our finding of 60% of GBS isolates to be serotype III is consistent with recent reports of the predominance of serotype III in LOD.[4] CPS is known to be an important virulence factor in GBS disease, and the hypervirulent clone CC17, which is found almost exclusively among serotype III isolates, contains the virulence factor *hvgA*, a surface-anchored adhesin that enables persistent colonization and predisposes to meningitis in neonates.[15] The majority (83%) of our capsular serotype III isolates were *hvgA* positive, but our nonserotype III isolates (Ia and Ib) were *hvgA* negative. This is consistent with findings from a recent study of 600 invasive GBS invasive infections in adults and children of all ages in the greater Toronto area (2009-2012), in which there was a significantly higher proportion of CPS type III in neonatal cases with LOD than in those with EOD.[16] In addition, it was shown that the vast majority of *hvgA*-positive strains were capsular type III. Thus, the clinical presentation of

Table III. Neuroradiographic findings and ACT

Case no.	Timing of MRI (days after LOD presentation)	MRI findings*	Vasculopathy	ACT	Bleeding complications
1	1	Multifocal, bilateral cortical ischemia and cerebellum. Ischemia of right ACA territory.	Irregular narrowing of right A1	Yes	No
2	2	Extensive ischemia of right MCA territory.	Severe right ICA stenosis	Yes	No
3	1	Multifocal, bilateral, cortical ischemia.	No	Yes	No
4	5	Multiple cortical foci of ischemia of left frontal and occipital lobes.	Focal narrowing of the proximal left A1	No	No
5	5	Ischemia involving right caudate and right mesial parietal lobe.	No	Yes for line related clot	No
6	2	Ischemia of right occipital lobe.	No	Yes	No
7	15	Multifocal, bilateral ischemia involving frontal and temporal lobes.	No	Yes for line related clot	No
8	2	Ischemia of inferior right frontal lobe	NA	No	No
9	6	Ischemia of left precentral gyrus and left occipital lobe.	No	No	No
10	4	Ischemia of left posterior inferior temporal and occipital lobes	No	Yes	Questionable (see discussion)
11	5	No ischemic lesion	Stenosis of distal VA to mid basilar artery. Stenosis of both cavernous ICA.	Yes	No
12	unknown	Ischemia of right parietal opercula.	NA	No	No
13	11	Multifocal, bilateral parietal ischemia	CSVT in transverse sinuses bilaterally, torcula, and right sigmoid.	Yes for CSVT	No
14	2	Multifocal, bilateral ischemia of frontal and temporal lobes.	No	Yes	Questionable (see discussion)

ACA, anterior cerebral artery; *ACT*, anticoagulation therapy; *ADC*, apparent diffusion coefficient; *DWI*, diffusion weighted imaging; *NA*, no magnetic resonance angiogram data available.
*All patients had positive DWI/ADC positive changes except case 12 where MRI timing could not be defined and case 13 who had negative DWI but positive T2 images.

meningitis in LOD may relate to the presence of this hypervirulent clone.

The mechanisms leading to cerebrovascular complications in bacterial meningitis are not completely understood and likely are multifactorial.[17] Invasion of the subarachnoid inflammatory exudate into the large vessels at the base of the brain may play a role. In addition, diverse bacterial components are powerful inducers of proinflammatory cytokines, possibly leading to vasculitis. Whether the serotype and certain virulence factors also predispose to cerebrovascular complications deserves further research. Vasospasm without evidence of inflammation on autopsy also has been described in adults with meningitis.[17] The pathophysiology of the cortical pattern of infarction observed in our cases as well as in recently published neonates with GBS-related strokes may be due to an inflammatory process in the small pial arteries, superficial cortical veins with venous infarction, or even direct extension of bacterial infection.[5]

Finally, infection also may lead to a hypercoagulable state. A rapid destruction of protein C and antithrombin III can be noted during serious infection. Down-regulation of thrombomodulin and upregulation of tissue factor have been described. A hypercoagulable state may explain the coexistence of arterial and venous occlusion in the same patient as observed in our series and in the previously published case.[12] Although a pre-existing prothrombotic condition theoretically might be an additional risk factor we were only able to identify a single case with elevated lipoprotein-A. Therefore, the causal role of thrombophilia seems to be limited.

There are not sufficient data to recommend any particular strategy of anticoagulation or antithrombotic treatment in cases of vasculopathy and stroke in the context of meningitis. However, in one of our patients (case 11) who did not have a stroke, the finding of significant basilar stenosis led to the decision to initiate anticoagulation for stroke prevention. This patient did not develop a stroke and no bleeding complication occurred. For cases in which ischemic injury already was present on the first MRI, it was decided to start anticoagulation in 9 children in order to prevent new strokes to treat a CSVT or a peripheral clot. Four of these patients were at a higher risk of recurrence resulting from severe vasculopathy. None of the treated patients had recurrent stroke or a significant bleeding complication. This is in agreement with a recently published study on anticoagulation of children with meningitis and stroke, in which significant bleeding complications did not occur.[18]

Our study has limitations including its retrospective design and, consequently, inconsistent follow-up programs, particularly regarding neurodevelopmental outcome and search for prothrombotic conditions. In addition, we were not able to provide robust incidence data on cerebrovascular diseases in GBS meningitis because of significant concerns of ascertainment bias. Multiple referral sites causing biases toward more severe cases, low rates of MRIs, and the lack of availability of CSF results of other invasive GBS cases that might have had meningitis are main limiting factors. In addition, the number of patients was relatively small which did not allow us to identify risk factors for cerebrovascular disease. Finally, the number of patients receiving anticoagulation therapy

was still too small to draw any final conclusion concerning safety and efficiency.

Late onset GBS meningitis can be complicated by severe cerebrovascular disease, including strokes and thromboses. The frequency of these complications might be underestimated. We recommend a low threshold for cerebral imaging, including vascular imaging, in order to detect vasculopathy and ischemic strokes early in the course of illness. Initiation of anticoagulant therapy in patients with LOD and cerebrovascular complications may be considered for secondary prevention. Future studies on the exact incidence, the role of GBS capsular types and virulence factors, and most importantly, on safety and efficiency of preventive anticoagulation therapy for patients with LOD-related strokes are warranted. ■

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Table I. Demographics and clinical features of cases of complicated late-onset GBS meningitis

Case no.	Age at onset (d)	Sex	Maternal GBS status	Gestational age at birth (wk)	Intubation in ICU	Use of inotropic drugs	Seizures at presentation	Electroencephalograph monitoring: subclinical seizures?	CNS complications	Developmental outcome
1	43	M	Negative	38	Yes	No	Left focal myoclonic	Yes	Hydrocephalus, VP-shunt	Normal at 7 mo
2	56	M	Negative	40	No	No	Left focal clonic	Yes	Microcephaly	Mild global delay at 11 mo
3	17	F	Unknown	38	Yes	Yes	No	Yes	Treatment resistant focal epilepsy	Hemiparesis, epilepsy surgery at 4 y
4	42	F	Negative	38	Yes	Yes	No	Yes	Infantile spasms	Global delay at 1 y
5	90	F	Negative	38	No	No	Gen. tonic clonic, left focal clonic	No	Subdural empyema	Mild speech delay at 2.3 y
6	8	M	Negative	38	No	No	Left focal clonic seizures	NA	Subdural hygroma	Normal at 6 mo
7	90	M	Negative	41	No	No	Right focal myoclonic seizures	Yes	Infantile spasms	Mild global delay at 3 y
8	70	M	Negative	30	Yes	Yes	Subtle	NA	None	Normal at 14 mo
9	12	M	Positive	39	Yes	Yes	Right focal myoclonic	Clinical seizures with CFM correlate	Hydrocephalus, VP-shunt	Normal at 2 y
10	17	M	Unknown	37	Yes	Yes	No	NA	None	Normal at 17 mo
11	18	F	Negative	40	Yes	Yes	Left focal clonic	NA	None	Normal at 12 mo
12	44	M	Negative	24	Yes	No	Yes	Yes (CFM)	None	Global delay, right hemiparesis at 13 mo
13	24	M	Positive	40	Yes	No	Yes	NA	Subdural empyema	Normal at 17 mo
14	30	F	Unknown	40	Yes	Yes	Yes	Yes	Subdural empyema	Normal at 22 mo

CFM, cerebral function monitoring; *CNS*, central nervous system; *F*, female; *ICU*, intensive care unit; *M*, male; *NA*, no electroencephalogram data available; *VP*, ventriculoperitoneal.