www.nature.com/clinicalpractice/neuro

A case of maternal herpes simplex virus encephalitis during late pregnancy

Johann Sellner, Roberto Buonomano, Krassen Nedeltchev, Oliver Findling, Gerhard Schroth, Daniel V Surbek and Stephen L Leib*

SUMMARY

Background A pregnant 25-year-old woman at 32 weeks' gestation was admitted to an emergency unit after her husband had found her drowsy and with her tongue bitten. The day before admission, the patient had developed a fever of 39 °C, was suffering from headaches, was nauseated and had vomited. On admission, she had anterograde and retrograde amnesia, but no somatic neurological deficits were detected.

Investigations Routine laboratory testing, lumbar puncture, cerebrospinal fluid analysis, routine bacteriology, brain MRI, and polymerase chain reaction testing for neurotropic viruses including herpes simplex virus types 1 and 2.

Diagnosis Maternal herpes simplex virus type 1 encephalitis.

Management Antiviral and anticonvulsive therapy, supportive treatment, and cesarean section.

KEYWORDS complications, encephalitis, herpes simplex virus type 1, pregnancy

CME

Medscape **Continuing Medical Education online**

Medscape, LLC is pleased to provide online continuing medical education (CME) for this journal article, allowing clinicians the opportunity to earn CME credit. Medscape, LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians. Medscape, LLC designates this educational activity for a maximum of 0.5 **AMA PRA Category 1 Credits**™. Physicians should only claim credit commensurate with the extent of their participation in the activity. All other clinicians completing this activity will be issued a certificate of participation. To receive credit, please go to **http://www.medscape.com/cme/ncp** and complete the post-test.

Learning objectives

Upon completion of this activity, participants should be able to:

1 Identify the most common viral cause of sporadic encephalitis in the United States.
2 Describe the clinical hallmark of acute viral encephalitis.
3 Identify the most common cause of neonatal herpes infection.
4 Describe the best radiologic test for detecting viral encephalitis.
5 Describe the diagnostic test of choice for detecting herpes simplex virus encephalitis.

Competing interests

The authors, the Journal Editor H Wood and the CME questions author D Lie declared no competing interests.

J Sellner is a Resident and Fellow in the Department of Neurology, Klinikum rechts der Isar at the Technical University of Munich, Munich, Germany. R Buonomano is Attending Physician for Internal Medicine at the County Hospital of Aarau, Aarau, K Nedeltchev is Consultant in the Department of Neurology at Triemli Municipal Hospital, Zurich, O Findling is a Resident in the Department of Neurology, G Schroth is Director of the Institute of Diagnostic and Interventional Neuroradiology, and DV Surbek is Acting Chairman of the Department of Obstetrics and Gynecology at Inselspital, University of Bern, and SL Leib heads the Laboratory for Experimental Neuroinfectiology in the Institute for Infectious Diseases at the University of Bern and is Attending Physician for Infectious Diseases at Inselspital, University of Bern, Bern, Switzerland.

Correspondence
*Institute for Infectious Diseases, University of Bern, Friedbuehlstrasse 51, CH-3010 Bern, Switzerland
stephen.leib@ifik.unibe.ch

Received 20 June 2008 **Accepted** 27 October 2008
www.nature.com/clinicalpractice
doi:10.1038/ncpneuro0972

THE CASE

A pregnant 25-year-old woman at 32 weeks' gestation was admitted to an emergency unit after her husband had found her drowsy and with her tongue bitten. The patient had anterograde and retrograde amnesia suggestive of a postictal state, indicating that she had experienced a first-ever generalized seizure. For the previous 3 days, she had been experiencing frontotemporal headaches associated with phonophobia and photophobia.

On the day before admission, the patient had developed a fever of 39 °C, was nauseated and had vomited. On admission, no somatic neurological deficits were detected. There were no signs of eclampsia as a possible underlying cause of the seizures—the patient's blood pressure was normal and proteinuria was absent. The patient had no history of genital lesions or their symptoms.

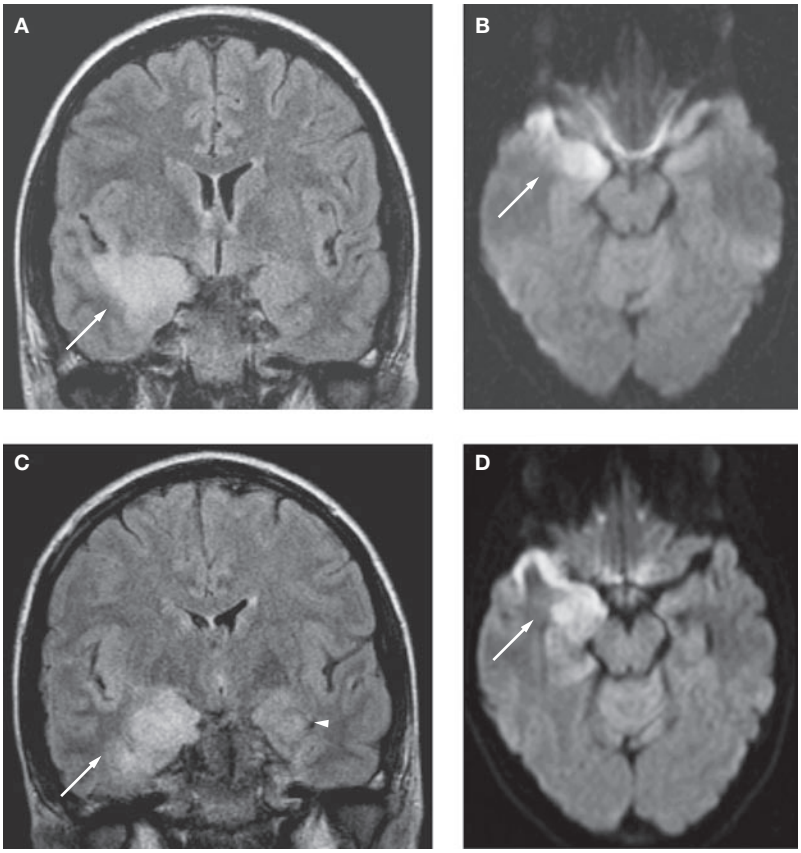

Figure 1 Brain MRI scans of a patient with acute herpes simplex type 1 encephalitis. (**A**) On admission, coronal FLAIR imaging showed T2 hyperintensities within the right temporopolar and temporomesial region (arrow). (**B**) Corresponding diffusion restriction was seen on axial diffusion-weighted sequences (arrow). (**C**,**D**) Repeat imaging was performed after the patient had experienced two further epileptic seizures and was somnolent. The right temporal lobe lesion was seen to have increased in size on the FLAIR sequences (**C**; arrow), and there was corresponding increased diffusion restriction, with the diffusion abnormalities now also involving the cortex (**D**; arrow). The repeat FLAIR images suggested that another lesion had appeared in the medial aspect of the left temporal lobe (**C**; arrowhead). No diffusion restriction was detected for this possible new lesion (**D**). Abbreviation: FLAIR, fluid-attenuated inversion recovery.

Laboratory examination of the patient's blood revealed leukocytosis (15.6×10^9 white blood cells/l; normal range 3.5–10.5×10^9 white blood cells/l) due to increased neutrophils (13.95×10^9 cells/l; normal range 1.6–7.4×10^9 cells/l), and raised levels of C-reactive protein (17 mg/l; normal value <5 mg/l).

Lumbar puncture was performed and cerebrospinal fluid (CSF) analysis revealed a pleocytosis with predominantly mononuclear cells (99%) of 125 cells/μl and 10 erythrocytes/μl, a normal protein level (0.37 g/l; normal value <0.42 g/l) and a slightly increased lactate level (2.3 mmol/l; normal value <2.1 mmol/l). A brain MRI scan with coronal fluid-attenuated inversion recovery (FLAIR) sequences revealed a temporopolar and mesial hyperintensity on the right side of the patient's brain (Figure 1A). On diffusion-weighted MRI sequences, the lesion showed areas of diffusion restriction (Figure 1B). Herpes simplex virus encephalitis (HSE) was suspected on the basis of the patient's medical history, clinical presentation, and CSF and MRI findings, and antiviral therapy with intravenous aciclovir (12.5 mg/kg every 8 h) was started, together with anticonvulsive prophylaxis consisting of four doses of 1 mg intravenous lorazepam administered at 6 h intervals. In addition, betamethasone (two doses of 12 mg given intramuscularly 24 h apart) was administered to stimulate lung maturation in the fetus. Polymerase chain reaction (PCR) testing of the patient's CSF was positive for herpes simplex virus type 1 (HSV-1) and negative for herpes simplex virus type 2 (HSV-2), confirming a diagnosis of HSV-1 encephalitis. Serology was negative for HSV-1 IgG, indicating that the patient had a primary herpes virus infection.

On the third day of hospitalization, the patient experienced a second generalized seizure, along with increasing drowsiness and meningeal signs, which prompted the instigation of intravenous anticonvulsive therapy with 100 mg lamotrigine once daily; this regimen was supplemented with 2.5 mg levetiracetam once daily after the patient had a third seizure on the fifth day of hospitalization. A second MRI scan at this point showed that the right-sided herpetic lesion had increased in volume and that signs of another lesion had appeared in the medial aspect of the left temporal lobe (Figure 1C). No diffusion restriction was detected for this possible new lesion (Figure 1D).

The deterioration of the patient's clinical status and the progression of the HSV-1 lesions in her brain led to concerns for the safety of the fetus, and a cesarean section was, therefore, performed under general anesthesia. No complications were experienced during the procedure, and a preterm but otherwise healthy infant (2,340 g birth weight) was delivered. The newborn was immediately started on aciclovir prophylaxis and was transferred to the neonatal intensive care unit. No viral copies were detected on HSV-1 PCR of the amniotic fluid, umbilical cord blood or venous blood of the infant drawn at delivery, and consequently its aciclovir prophylaxis was discontinued.

The mother experienced no further seizures and her aciclovir therapy was stopped 21 days after its initiation when her PCR results from a second

Table 1 Reports on maternal herpes simplex virus type 1 encephalitis during pregnancy made available during the period 1986–2006.

Year	Maternal age (years)	Gestation week	Initial neurological symptom	Diagnostic method	Antiviral treatment (duration)	Delivery method (week)	Recorded outcomes of mother and fetus
1986[13]	39	28	Seizure	Brain biopsy and serum antibody titers	Aciclovir 15 mg/kg every 8 h (10 days)	Cesarean section (30)	Unknown for mother (coma); fetus survived
1987[14]	22	29	Seizure	Serum antibody titers	Aciclovir 800 mg/day (22 days)	Spontaneous (39)	Both survived
1989[15]	25	23	Somnolence	Serum antibody titers	Aciclovir 10 mg/kg every 8 h (10 days)	Spontaneous (39)	Both survived
1999[5]	35	27	Seizure	CSF PCR	Aciclovir (dosage and duration unknown)	Spontaneous (term)	Both survived
1999[5]	31	35	Abnormal behavior, hallucinations, aphasia	CSF PCR	Aciclovir (dosage and duration unknown)	Spontaneous (term)	Both survived
2006 (present case)	25	32	Seizure	CSF PCR	Aciclovir 12.5 mg/kg every 8 h (21 days)	Cesarean section (33)	Both survived
2006 (J Sellner *et al.*, unpublished data)	26	30	Aphasia	CSF PCR	Aciclovir 10 mg/kg every 8 h (14 days)	Spontaneous (33)	Both survived

Abbreviation: CSF PCR, polymerase chain reaction testing of the cerebrospinal fluid.

CSF examination were negative for HSV-1. Other findings were a 98% mononuclear pleocytosis of 40 cells/μl, a protein level of 0.51 g/l and a lactate level of 1.4 mmol/l. No neurological or neuropsychological deficits were present in the mother or her newborn infant at discharge 4 weeks after initial hospitalization. The mother did not experience any further seizures, but anticonvulsive prophylaxis with lamotrigine was continued until the first follow-up 6 months after discharge.

DISCUSSION OF DIAGNOSIS

Over 100 different viruses have been associated with acute CNS infections.[1] HSV-1 is the most common cause of acute sporadic encephalitis in the US, being responsible for approximately 10–20% of cases.[2] About a third of cases of HSV-1 encephalitis that occur beyond the neonatal period are caused by primary HSV-1 infection, and approximately two-thirds result from viral reactivation of HSV-1. The clinical hallmark of acute viral encephalitis is a triad of fever, headache and altered mental state.[2] Other common findings at presentation and during the course of viral encephalitis include disorientation, behavioral and speech disturbances, and focal or diffuse neurological signs such as hemiparesis or seizures. In the present case, a first-episode primary infection with HSV-1 was suggested by the negative findings for HSV-1 IgG on blood serology. HSV-1 preferentially involves the temporal lobe, so clinical symptoms of HSV-1 encephalitis frequently include aphasia, anosmia, temporal lobe seizures and other focal abnormalities.[2] CSF abnormalities in patients with viral encephalitis include pleocytosis with predominantly mononuclear cells, and increased protein levels. A small percentage (<5%) of patients can, however, have a completely normal CSF profile.[2] Early diagnosis of HSV-1-associated HSE and prompt initiation of treatment is crucial to reduce mortality and improve outcome.[3]

Pregnancy predisposes for viral infections, and these infections are associated with potential harm to both mother and fetus.[4] However, maternal HSE during pregnancy is rare, and the risk of initial misdiagnosis is high.[5] According to the reports available (Table 1), the most probable time of occurrence of maternal HSV-1 encephalitis is between the late second and early third trimester of pregnancy. Infection during this time can result in fetal growth retardation, fetal loss, or premature labor.[6] It remains unclear why pregnant women are particularly susceptible to viral infection, and HSV-1 in particular, at this point in their pregnancy, although one contributing factor might be physiological immunosuppression, leading to attenuated natural-killer-cell cytotoxicity, during late pregnancy.[6]

Herpes infection in neonates can be caused by HSV-1 or HSV-2 and often has debilitating or fatal

consequences. Controversies remain regarding how to define HSV infection in neonates. There are three classical presentations: mucocutaneous, disseminated, and isolated CNS disease.[6] Most cases (about 85%) of neonatal herpes infection are caused by HSV-2 acquired from herpetic lesions in the maternal genital tract at the time of vaginal delivery.[7] An additional 10% of neonatal HSV infections are acquired after delivery, and the remaining 5% of cases are caused by infection *in utero*.[8] A third of all neonates with HSV infection will have CNS involvement and seizures as the most frequent presenting symptom.[9]

The outlook following HSV-1 encephalitis used to be poor for both mother and fetus;[10,11] however, the use of aciclovir on suspicion of the disease, combined with advances in critical care and diagnostic procedures, means that favorable outcomes may now be achieved for both.[7–9,12] A PubMed search for confirmed maternal HSV-1 encephalitis reports from 1986 to 2006 revealed only five published cases;[5,13–15] another case is known of, in a patient treated in 2006 at the same institution as the case patient (J Sellner *et al.*, unpublished data). All of the patients received intravenous aciclovir, and all mothers for whom outcome was reported, and all neonates, survived (Table 1). Yet, long-term neurological sequelae, including memory impairment, personality and behavioral abnormalities, and epilepsy, are a major concern,[16] and in the reported cases aciclovir treatment was shown mainly to influence mortality and to be less effective at reducing morbidity in both HSV-1 and HSV-2 encephalitis.[10]

MRI scanning and CSF examination are the mainstays of the diagnostic work-up for suspected viral encephalitis. MRI is more sensitive than CT for detecting encephalitic changes and might also rule out other potential diseases.[17] Gadolinium-enhanced MRI is particularly sensitive at visualizing lesions in viral encephalitis but was not performed in the present case in view of the relative contraindications for applying contrast agents during pregnancy.[18] Diffusion-weighted MRI, which was used here, can distinguish between cytotoxic and vasogenic edema and can provide better lesion detection at early disease stages than can standard MRI.[19] Brain MRI scans can also aid in the monitoring of lesion evolution and possible intracerebral complications. Repeat MRI scans can be performed in cases of clinical deterioration with reduced level of consciousness or recurrent seizures. The MRI findings of a temporopolar and mesial hyperintensity in the current patient are congruent with the characteristic MRI findings in HSV-1-associated HSE, including T2-weighted hyperintensities that lie within the mesial and inferior temporal lobes and extend into the insula.[17] In immunosuppressed patients and infants, HSE can produce different MRI findings, including involvement of the cortex and adjacent white matter, and sparing of the temporal lobe.[20]

PCR testing of the CSF has supplanted brain biopsy as the modality of choice for diagnosing HSV CNS disease. In adults, the sensitivity of PCR for detecting HSV-1 in patients with encephalitis exceeds 95%, and the specificity approaches 100% compared with brain biopsy.[21] The sensitivity is, however, lower in neonates, at around 75%.[21] In addition, PCR tests can produce false negative results, particularly when performed early in the disease course (<3 days after initial symptoms).[22]

DIFFERENTIAL DIAGNOSIS

Clinically, infectious diseases of the CNS can present with unspecific symptoms including headaches, nausea and fever. Thus, bacterial and fungal infections should be considered in the differential diagnosis of acute viral encephalitis. Patients are often empirically treated for a potential infection with bacterial and viral pathogens with both antibiotics and antiviral agents until the diagnosis of HSE has been established. Predominantly lymphocytic or monocytic pleocytosis in the CSF can be present in tuberculous or fungal CNS infection as well as in HSE; however, the former infections are associated with a dramatic elevation in protein levels and with hypoglycorachia, which are not typical for HSE.

Many other viruses, including cytomegalovirus, influenza A and echovirus, have been shown to affect the temporal lobe and to mimic HSE, and HSE has no particular clinical characteristics to distinguish it from other CNS infections. Additionally, HSV-2 is a putative cause of HSE, and a 2008 study reported that 12% of all CNS infections with HSV-2 are encephalitic and often have neurological sequelae.[23] Tumors, brain abscesses and hematomas can also mimic HSE.[2] In addition, vascular disorders and toxic encephalopathies can be mistaken for HSE.

TREATMENT AND MANAGEMENT

The standard recommended first-line treatment for HSE in adults is intravenous aciclovir 10 mg/kg every 8 h.[24] Some authors even recommend

higher doses of 15–20 mg/kg every 8 h.[24] In neonates, doses of up to 20 mg/kg every 8 h have been recommended.[25] The pharmacokinetics of aciclovir in full-term pregnant women have been well described; serum aciclovir levels are similar between the mother and fetus, but in the amniotic fluid the drug can be concentrated to up to four times the serum level.[26] In one study, no increased rate of birth defects was shown for pregnancies exposed to aciclovir in the third trimester, which is remarkable given that this agent inhibits a human DNA polymerase.[27]

The recommended duration of intravenous aciclovir treatment is 14 days in immunocompetent, and 21 days in immunosuppressed, adult patients with HSE, and 21 days in neonates.[6] Antiviral treatment can be stopped after completion of the recommended therapeutic period. As done in the current patient, some studies recommend performing a second lumbar puncture to demonstrate the absence of viral copies in the CSF after completion of therapy. Aciclovir should not be stopped before completion of the recommended duration as shorter treatment periods are associated with a high risk of relapse of HSE.[24] In pregnant women who are clinically stable, intravenous aciclovir can be used to treat HSE while spontaneous delivery is awaited. In patients with a previous history of genital HSV infection and in mothers who experienced a first episode of genital herpes during the last trimester of gestation, prophylactic administration of valaciclovir, a prodrug of aciclovir, during the 4 weeks preceding delivery has been shown to reduce the number of recurrences of genital HSV at term and, thereby, also the need for cesarean section. Hence, prophylactic treatment with valaciclovir is recommended in these patient groups.[28]

In HSE, if the clinical condition of the mother and/or the fetus deteriorates, cesarean section is an option both for saving the life of the child and for enabling intensification of treatment for the mother and the child. Cesarean section was performed in the present patient because of her recurrent seizures. Continuing epileptic seizures are a major concern during pregnancy, as they might result in the need for mechanical ventilation, and additionally the potential therapy escalation with conventional antiepileptics is restricted during pregnancy because of potential harmful effects to the fetus.

For recurrent seizures in nonpregnant women, high-dose intravenous phenytoin or valproate are the first-line therapies, and the treatment is continued with an oral formulation of the drug that was used for intravenous therapy.[29] Neither of these drugs is recommended as a first-line treatment during pregnancy, however, as both are associated with an increased risk of teratogenesis. First-line antiepileptic treatment during pregnancy is limited mainly to lamotrigine and benzodiazepines (lorazepam in the present case).

Supportive treatment is the cornerstone of management of acute viral encephalitis[24] and was undertaken in the case patient. It is vital to maintain fluid balance and to be aware of possible secondary complications such as pneumonia and deep-vein thrombosis. Other acute intracerebral complications of HSE, such as raised intracranial pressure and cerebrovascular complications, can also threaten the lives of the mother and fetus.[24] The occurrence of abnormal behavior in the mother, with personality change or altered consciousness, can increase the risk of complications during pregnancy and might strengthen the case for preterm delivery by cesarean section. Current guidelines suggest that high-dose steroids can be given concomitantly with aciclovir in cases of progressive deterioration of consciousness.[24]

In the present case, fetal surveillance was performed with ultrasound scanning and cardiotocography to detect possible fetal signs of infection or nonreassuring fetal biophysical status. Betamethasone was given to the mother to promote fetal pulmonary maturation. Aciclovir prophylaxis was given to the infant, which was stopped when no evidence of HSV-1 infection was detected in the neonate. The standard evaluation of neonates with known HSV exposure includes culture of eye, throat and rectal swabs. Any suspicious skin lesion should be evaluated by direct fluorescent antibody assay, and the CSF should be checked biochemically and cytologically and by HSV PCR analysis.[9]

CONCLUSIONS

Maternal HSE during pregnancy is a medical challenge that requires a multidisciplinary approach for treatment of the maternal disease and prevention of infection in the neonate. The dosage and duration of antiviral treatment in the mother and neonate, symptomatic treatment of acute complications, and timing and route of neonate delivery, all need to be considered. With an early diagnosis and prompt initiation of antiviral treatment, as well as enhanced neurocritical care, a favorable outcome can now be expected in both mother and child.

Acknowledgments

The authors appreciate the assistance of Dr A Tofield for his proofreading and editing of the English language in this manuscript. Written consent for publication was obtained from the patient. J Sellner and R Buonomano have contributed equally to this manuscript. Désirée Lie, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the Medscape-accredited continuing medical education activity associated with this article.

Competing interests

The authors declared no competing interests.

References

1 Hinson VK and Tyor WR (2001) Update on viral encephalitis. *Curr Opin Neurol* **14:** 369–374
2 Whitley RJ and Gnann JW (2002) Viral encephalitis: familiar infections and emerging pathogens. *Lancet* **359:** 507–513
3 Raschilas F *et al.* (2002) Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. *Clin Infect Dis* **35:** 254–260
4 Ornoy A and Tenenbaum A (2006) Pregnancy outcome following infections by coxsackie, echo, measles, mumps, hepatitis, polio and encephalitis viruses. *Reprod Toxicol* **21:** 446–457
5 Dupuis O *et al.* (1999) Herpes simplex virus encephalitis in pregnancy. *Obstet Gynecol* **94:** 810–812
6 Malkin JE and Beumont MG (1999) Herpes simplex virus infection in pregnancy. *Herpes* **6:** 50–54
7 Mertz GJ (1993) Epidemiology of genital herpes infections. *Infect Dis Clin North Am* **7:** 825–839
8 Hutto C *et al.* (1987) Intrauterine herpes simplex virus infections. *J Pediatr* **110:** 97–101
9 Whitley R (2004) Neonatal herpes simplex virus infection. *Curr Opin Infect Dis* **17:** 243–246
10 Engman ML *et al.* (2008) Neuropsychologic outcomes in children with neonatal herpes encephalitis. *Pediatr Neurol* **38:** 398–405
11 Mudido P *et al.* (1993) Disseminated herpes simplex virus infection during pregnancy: a case report. *J Reprod Med* **38:** 964–968
12 Nahmias AJ *et al.* (1970) Infection of the newborn with herpesvirus hominis. *Adv Pediatr* **17:** 185–226
13 Greffe BS *et al.* (1986) Transplacental passage of acyclovir. *J Pediatr* **108:** 1020–1021
14 Hankey GJ *et al.* (1987) Herpes simplex encephalitis in third trimester of pregnancy: successful outcome for mother and child. *Neurology* **37:** 1534–1537
15 Besser R *et al.* (1989) Successful treatment of HSV encephalitis during pregnancy. *Neurology* **39:** 748
16 McGrath N *et al.* (1997) Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. *J Neurol Neurosurg Psychiatry* **63:** 321–326
17 Schroth G *et al.* (1987) Early diagnosis of herpes simplex encephalitis by MRI. *Neurology* **37:** 179–183
18 Garcia-Bournissen F *et al.* (2006) Safety of gadolinium during pregnancy. *Can Fam Physician* **52:** 309–310
19 McCabe K *et al.* (2003) Diffusion-weighted MRI abnormalities as a clue to the diagnosis of herpes simplex encephalitis. *Neurology* **61:** 1015–1016
20 Leonard JR *et al.* (2000) MR imaging of herpes simplex type 1 encephalitis in infants and young children: a separate pattern of findings. *AJR Am J Roentgenol* **174:** 1651–1655
21 Lakeman FD and Whitley RJ (1995) Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease: National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *J Infect Dis* **171:** 857–863
22 De Tiège X *et al.* (2003) Limits of early diagnosis of herpes simplex encephalitis in children: a retrospective study of 38 cases. *Clin Infect Dis* **36:** 1335–1339
23 Omland LH *et al.* (2008) Herpes simplex virus type 2 infections of the central nervous system: a retrospective study of 49 patients. *Scand J Infect Dis* **40:** 59–62
24 Steiner I *et al.* (2005) Viral encephalitis: a review of diagnostic methods and guidelines for management. *Eur J Neurol* **12:** 331–343
25 Kimberlin DW (2007) Herpes simplex virus infections of the newborn. *Semin Perinatol* **31:** 19–25
26 Frenkel LM *et al.* (1991) Pharmacokinetics of acyclovir in the term human pregnancy and neonate. *Am J Obstet Gynecol* **164:** 569–576
27 Stone KM *et al.* (2004) Pregnancy outcomes follwowing systemic prenatal acyclovir exposure: conclusions from the international acyclovir pregnancy registry, 1984–1999. *Birth Defects Res A Clin Mol Teratol* **70:** 201–207
28 Sheffield JS *et al.* (2006) Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial. *Obstet Gynecol* **108:** 141–147
29 Abou Khaled KJ and Hirsch LJ (2008) Updates in the management of seizures and status epilepticus in critically ill patients. *Neurol Clin* **26:** 385–408, viii