CASE REPORT

In-hospital herpes simplex encephalitis after open heart surgery: an emerging pathology or an under-recognised condition?

Mohamed Saleh

Department of Critical Care,
Pitié Salpêtrière Hospital, Paris,
France

Correspondence to
Dr Mohamed Saleh,
bpco20032002@yahoo.fr

SUMMARY

Two patients developed herpetic encephalitis after cardiopulmonary bypass for two different surgical indications. Diagnosis was extremely difficult. Both patients recovered under antiviral treatment despite late diagnosis.

BACKGROUND

During cardiac surgery with cardiopulmonary bypass (CPB), the development of a systemic inflammatory response has been well established.^{1 2} The levels of inflammatory mediators, including interleukin 6 (IL-6), IL-8 and tumour necrosis factor- α , considerably increase and reach their peak levels 2–4 h after termination of CPB.³ Herpes simplex virus (HSV) is the most common cause of sporadic encephalitis throughout the world. Even with adequate treatment, this infection is associated with a mortality rate of 19–30% and important neurological after effects among survivors.⁴

Herpes simplex encephalitis develops when HSV infects brain tissue in a lytic/necrotic manner.⁵ Although both primary and recurrent HSV infections may lead to encephalitis, most HSV encephalitis cases in adults are due to reactivation of latent viruses.⁶ Many factors including inflammatory stress can promote HSV reactivation.

Inflammatory stress induced by surgery may be a triggering factor for herpes reactivation. Postoperative HSV encephalitis has been described following neurosurgical procedures on rare occasions,^{7–9} but HSV encephalitis after cardiac surgery had never been reported.

These two observations pointed out the difficulty to establish the diagnosis in such context.

CASE PRESENTATION**First patient**

A 45-year-old male patient was admitted in our intensive care unit (ICU) after heart–kidney transplantation. He had a medical history of severe dilated alcoholic cardiomyopathy complicated by terminal heart failure and terminal renal failure due to chronic bilateral pyelonephritis. He had 120 min CPB for heart transplantation followed by renal transplantation. Surgery was uneventful. He was weaned from mechanical ventilation 24 h later and had low doses of norepinephrine to enhance his renal allograft perfusion. Renal graft worked initially well with 1 L/day estimated urine output.

Immunosuppressive regimen consisted of methylprednisolone (40 mg/day) and mofetil mycophenolate (1000 mg/day). On the third postoperative day, he developed anuric renal failure and septic shock. He was transferred to our ICU for management. The patient needed mechanical ventilation because of septic shock-related encephalopathy. The origin of septic shock seemed to be related to *Candida albicans* found in renal allograft preservation solution. It was successfully treated by fluconazole intravenous infusion. Ultrasound control of renal allograft showed no vascular or obstructive abnormalities. On the fourth postoperative day immunosuppressive protocol consisted of adjunction of antihuman lymphocyte serum. On the ninth postoperative day the patient's medical situation allowed weaning from mechanical ventilation and norepinephrine.

On the 10th postoperative day his state of consciousness altered and rapidly progressed to coma associated with fever and septic shock necessitating mechanical ventilation and circulatory support by norepinephrine. No biological findings could explain this coma.

Second patient

A 68-year-old male patient admitted to our ICU after CPB for aortocoronary bypass surgery. He had a medical history of chronic hypertension treated by a β blocker agent.

Otherwise he had no other remarkable medical condition. He had an emergency aortocoronary bypass surgery for an acute myocardial infarction. The surgery consisted of four venous grafts between coronary network and ascending aorta. The surgery was uneventful and the patient was weaned from mechanical ventilation immediately after surgery.

On the next day he developed respiratory failure and pneumonia. He was admitted in our ICU for management. On admission his temperature was 39°C, arterial blood pressure was maintained at 120/90 mm Hg by epinephrine 0.5 mg/h. He was under mechanical ventilation (Fio₂ 50%).

Pulmonary auscultation showed bilateral basal crackles. There were no other pathological findings on clinical examination. The patient was already treated by piperacillin–tazobactam and amikacin. On the fifth day of admission he was weaned from mechanical ventilation and epinephrine. Since then, he presented with altered mental status characterised by visual hallucinations alternating with

To cite: Saleh M. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009737

aggressive behaviour. There were no explanation for his condition and no clinical or laboratory signs of sepsis.

On the sixth day of admission he had right hypochondrial pain; abdominal ultrasound showed gall bladder distension. Gall bladder ablation was then performed. The patient's mental status still remained abnormal.

INVESTIGATIONS

First patient

We proceeded to emergency lumbar puncture because of comatose febrile state. Cerebrospinal fluid (CSF) analysis showed 28 elements (monocytes 50%, neutrophils 30% and rare lymphocytes). CSF proteins and CSF glucose levels were normal. Gram stain was negative. The patient received acyclovir intravenous infusion.

Next day CSF herpes simplex type 1 PCR was positive. Other herpes group virus PCRs were negative. No fungal agent was found and CSF culture remained negative.

Second patient

Brain CT was normal. Brain MRI was performed on the ninth day of admission and was normal. Lumbar puncture was performed on the ninth day of admission; it showed no cellular elements and CSF proteins and glucose levels were normal. Gram stain and bacterial culture were negative but herpes simplex type 1 was detected in large amounts by PCR in CSF.

TREATMENT

First patient

The patient received acyclovir intravenous infusion once CSF was withdrawn.

Second patient

The patient received intravenous acyclovir infusion once HSV was detected.

OUTCOME AND FOLLOW-UP

First patient

Four days after acyclovir treatment the patient recovered with a normal neurological status with no sequelae; he was weaned from catecholamine and mechanical ventilation, and was discharged. Antiviral treatment was pursued for 21 days.

Second patient

The patient regained normal mental status within 4 days of antiviral treatment. The treatment was pursued for 21 days.

DISCUSSION

To our knowledge this is the first report of occurrence of in-hospital HSV encephalitis after CPB surgery.

When analysing predisposing factors we might assume for our first patient that immunosuppressive therapy played a role.

However, the brief delay between instauration of immunosuppressive treatment and the diagnosis of HSV encephalitis does not support a predominant role of immunosuppressant treatment in the disease process.

In reviewing 432 patients with presumptive HSV encephalitis and by searching for virus via brain biopsy and comparing biopsy findings with CSF findings in patients with biopsy-proven HSV encephalitis (195/432), Whitley *et al*¹⁰ found CSF abnormalities in nearly all patients (97%) and fever in 90% of cases.

Our second patient had no fever and no CSF abnormalities at the time of diagnosis and his brain MRI was normal and unless HSV PCRs were available, diagnosis of viral encephalitis would

have never been established. This unique finding highlights the importance of clinical presumption and the role of molecular biology in establishing HSV encephalitis.

The most probable differential diagnosis concerning our second patient was postcardiotomy delirium (PCD).

In general postoperative delirium of non-cardiac surgery has been associated with increased mortality,¹¹ functional decline¹² and increased cost.¹³ Despite the high prevalence and negative sequelae of postoperative delirium, its pathophysiology remains unknown.¹⁴

In a recent review on PCD there were no mention of relationship between HSV and PCD.¹⁵ However, untreated HSV-associated delirium would be fatal.

These two case reports highlighted the clinical polymorphism of HSV encephalitis presentation and the challenging diagnosis of this pathology in the postoperative context.

We showed that true HSV encephalitis might be present even with normal standard CSF analysis and MRI brain images.

Only diagnosis by molecular biology has been life-saving for our patients.

Learning points

- In the context of cardiopulmonary bypass, herpes simplex virus (HSV) encephalitis should be ruled out once unexplained postoperative altered mental status or behaviour develops before talking about delirium because any delay in antiviral treatment influences neurological outcome.
- It cannot be excluded that severe forms of delirium might be due to under-recognised HSV encephalitis.
- This can be supported by the recent recognition of HSV as a causal agent of a number of otherwise unexplained central nervous system conditions like Mollaret's meningitis,^{16–18} progressive dementia syndrome¹⁹ and chronic encephalitis.²⁰

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Cameron D. Initiation of white cell activation during cardiopulmonary bypass: cytokines and receptors. *J Cardiovasc Pharmacol* 1996;27(Suppl 1):S1–5.
- 2 Morse DS, Adams D, Magnani B. Platelet and neutrophil activation during cardiac surgical procedures: impact of cardiopulmonary bypass. *Ann Thorac Surg* 1998;65:691–5.
- 3 Wan S, Marchant A, DeSmet JM, *et al*. Human cytokine responses to cardiac transplantation and coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 1996;111:469–77.
- 4 Schmutzhard E. Viral infections of the CNS with special emphasis on herpes simplex infections. *J Neurol* 2001;248:469–77.
- 5 Studahl M, Rosengren L, Gunter G, *et al*. Difference in pathogenesis between herpes simplex virus type 1 encephalitis and tick-borne encephalitis demonstrated by means of cerebrospinal fluid markers of glial and neuronal destruction. *J Neurol* 2000;247:636–42.
- 6 Johnson RT. *Viral infections of the nervous system*. 2nd edn. Philadelphia, New York: Lippincott-Raven, 1998.
- 7 Spuler A, Blaszyk H, Parisi JE, *et al*. Herpes simplex encephalitis after brain surgery: case report and review of the literature. *J Neurol Neurosurg Psychiatry* 1999;67:239–42.
- 8 Fearnside MR, Grant JMF. Acute necrotizing encephalitis complicating bifrontal craniotomy and pituitary curettage. *J Neurosurg* 1972;36:499–502.
- 9 Aldea S, Joly LM, Roujeau T, *et al*. Postoperative herpes simplex virus encephalitis after neurosurgery: case report and review of the literature. *Clin Infect Dis* 2003;36:e96–9.

- 10 Whitley RJ, Cobbs CG, Alford CA, *et al.* Diseases which mimic herpes simplex encephalitis: diagnosis, presentation, and outcome. *JAMA* 1989;262:234–9.
- 11 Marcantonio ER, Goldman L, Mangione CM, *et al.* A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA* 1994;271:134–9.
- 12 Marcantonio ER, Flacker JM, Michaels M, *et al.* Delirium is independently associated with poor functional recovery after hip fracture. *J Am Geriatr Soc* 2000;48: 618–24.
- 13 Franco K, Litaker D, Locala J, *et al.* The cost of delirium in the surgical patient. *Psychosomatics* 2001;42:68–73.
- 14 Inouye SK. Delirium in older persons. *N Engl J Med* 2006;354:1157–65.
- 15 Sockalingam S, Parekh N, Bogoch II, *et al.* Delirium in the postoperative cardiac patient: a review. *J Card Surg* 2005;20:560–7.
- 16 Bachmeyer C, de la Blanchardiere A, Lepercq J, *et al.* Recurring episodes of meningitis (Mollaret's meningitis) with one showing an association with herpes simplex virus type 2. *J Infect* 1996;32:247–8.
- 17 Gignoux L, Ryvling P, Najjoulah F, *et al.* Recurrent Mollaret's meningitis of herpetic origin. *Presse Med* 1998;27:1470–2.
- 18 Jensenius M, Myrvang B, Storvold G, *et al.* Herpes simplex virus type 2 DNA detected in cerebrospinal fluid of 9 patients with Mollaret's meningitis. *Acta Neurol Scand* 1998;98:209–12.
- 19 Zachhuber C. Necrotizing herpes simplex encephalitis as the cause of a progressive dementia syndrome. *Dtsch Med Wochenschr* 1995;120:1278–82.
- 20 Sage JI. Chronic encephalitis possibly due to herpes simplex virus: two cases. *Neurology* 1985;35:1470–2.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow