

Severe neurologic manifestations in acute intermittent porphyria developed after spine surgery under general anesthesia -a case report-

Eun Young Park, Yi Seul Kim, Kyung-Jee Lim, Hye Kyoung Lee, Soo Kyung Lee, Hyun Choi, and Mae-Hwa Kang

Department of Anesthesiology and Pain Medicine, Hallym University College of Medicine, Anyang, Korea

Porphyrias are inherited metabolic disorders resulting from a specific enzyme defect in the heme biosynthetic pathway. Porphyrias are induced by various precipitants. Clinical features include abdominal pain, neurologic manifestations, autonomic neuropathy, and mental disturbance. Diagnosis may be delayed because of variable symptoms that mimic other diseases and because of the rarity of porphyrias. Although most patients with known porphyria can complete anesthesia and surgery safely, undiagnosed porphyric patients are in danger of porphyric crisis due to inadvertent exposure to precipitating drugs and environment. We report a case of a patient who experienced delayed emergence with neurological disturbance after general anesthesia, ultimately diagnosed as acute intermittent porphyria. (Korean J Anesthesiol 2014; 67: 217-220)

Key Words: Delayed emergence from anesthesia, General anesthesia, Guillain-Barre Syndrome, Porphyrias, Wernicke encephalopathy.

Porphyrias are rare genetic diseases characterized by aberrations in the heme synthetic pathway, which result in the accumulation of precursor molecules in tissue [1]. Acute intermittent porphyria (AIP) is the most common type and has the most severe symptoms of all the porphyrias. An acute episode can be triggered by surgery, certain drugs, pregnancy, menstruation, infection, and fasting [2]. In AIP, the typical pattern consists of acute attacks of abdominal pain, autonomic nervous system instability, electrolyte disturbance, and neuropsychiatric mani-

festations ranging from mild to life-threatening [3]. We report a case of postoperative presentation of AIP in an undiagnosed patient after posterior lumbar interbody fusion (PLIF).

Case Report

A 75-year-old female patient (height 141 cm, weight 44 kg) visited the emergency room with low back pain and radiating pain, and was admitted for further evaluation. She was diag-

Received: July 10, 2013. Revised: August 7, 2013. Accepted: August 22, 2013.

Corresponding author: Mae-Hwa Kang, M.D., Ph.D., Department of Anesthesiology and Pain Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, 22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 431-796, Korea. Tel: 82-31-380-5959, Fax: 82-31-385-3244, E-mail: drberry@hanmail.net

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

nosed with spinal stenosis and was scheduled to undergo L4-5-S1 PLIF. Ten days prior to the current admission, the patient presented abdominal pain accompanied by nausea and poor oral intake. A diagnostic workup including abdominal computed tomography (CT) and upper gastrointestinal endoscopy were normal. She was discharged after improving with conservative management.

She did not have underlying disease and family history of neuromuscular disease. The preoperative electrocardiogram revealed nonspecific ST and T wave change, and an echocardiogram was within normal limits. Chest radiograph and routine laboratory findings were normal. Upon arrival in the operating room, the patient's blood pressure was 130/80 mmHg, heart rate was 115 beats/min and pulse oxygen 92%. She was premedicated with intramuscular glycopyrrolate 0.2 mg before the surgery. After standard monitoring, general anesthesia was induced with pentothal sodium 175 mg, rocuronium 35 mg and remifentanyl 0.05 µg/kg/min. Endotracheal intubation was performed using a light-wand. After induction of anesthesia, arterial cannulation was performed with a 20 G catheter in the right radial artery, and central venous cannulation was performed in the right internal jugular vein. Anesthesia was maintained with desflurane, a mixture of oxygen and air (FiO₂ 0.5) and intravenous infusion of remifentanyl. The concentration of desflurane was controlled to maintain the bispectral index within 40–60. Warm forced air devices were used to maintain body temperature.

Throughout the operation, the patient showed no specific abnormalities of her vital signs. Phenylephrine 50 µg/min was infused to maintain the systolic blood pressure between 90 and 110 mmHg. The blood loss was about 1,000 ml and 2,150 ml of crystalloid solution, 500 ml of colloid solution and three pints of packed red blood cells were administered. The surgery was completed uneventfully and the anesthesia lasted 310 min. Core body temperature measured with esophageal stethoscope was around 36°C during the operation. The neuromuscular blockade was reversed with glycopyrrolate 0.4 mg and neostigmine 1.5 mg at the end of the procedure. However, the patient presented with significantly delayed emergence from anesthesia. The patient was drowsy and needed assisted ventilation due to weak spontaneous respiratory efforts during the 40 min after surgery. At the time, arterial blood gas analysis revealed pH, 7.23; PaCO₂, 41 mmHg; PaO₂ 284 mmHg; HCO₃, 17.2 mEq/L and SaO₂ 100%. Other laboratory examinations revealed sodium 138 mmol/L, potassium 4.9 mmol/L, calcium 1.18 mmol/L, Hb 9.9 g/dl and glucose 112 mg/dl. No specific laboratory values to explain the delayed emergence were noted. The patient was transferred to the intensive care unit in an intubated state. Although she was extubated at the intensive care unit after 30 min, she remained minimally arousable. Motor power was reduced from grade IV (mild weakness) to grade I (visible contraction but no move-

ment) in bilateral upper and lower extremities, but no sensory loss was observed. Cervical spine magnetic resonance imaging (MRI), brain MRI and electroencephalography (EEG) were performed on the recommendation of a neurologist on postoperative day (POD) 1. Cervical spine MRI was normal. Brain lesions in bilateral post central gyrus, medial thalami, periventricular region, periaqueductal region and hypothalamus in brain MRI were suggestive of Wernicke's encephalopathy (WE). Accordingly, she was started on vitamin B1, but her motor functions and mental status did not recover. EEG showed diffuse cerebral dysfunction. On POD 10, nerve conduction study and electromyography demonstrated axonal dominant sensorimotor polyneuropathy. The neurologist then considered Guillain-Barre Syndrome (GBS) and treated with intravenous immunoglobulin. The patient was intubated due to the continuous respiratory muscle weakness and pulmonary infection led to respiratory failure requiring mechanical ventilation. On POD 12, hyponatremia (118 mmol/L) and clinical epileptic form discharge on EEG were detected. Symptomatic treatment was eventually with phenytoin and hypertonic saline.

The patient showed mental change and motor axonal peripheral neuropathy simultaneously, and presented abdominal pain, nausea and poor oral intake before the surgery. She also showed labile blood pressure (60–188/44–120 mmHg) and tachycardia (100–136 beats/min) suggestive of autonomic dysfunction, respiratory muscle weakness due to peripheral neuropathy and hyponatremia. These findings suggested AIP and the diagnosis was ascertained from detecting high urine porphobilinogen on POD 13. Glucose infusion was given to the patient, with a plan to administer heme arginate if the symptoms persisted.

Although her motor power was gradually improved, her general condition deteriorated rapidly with aggravating pneumonia and she expired on POD 35.

Discussion

Porphyrias are a group of inborn metabolic disorders that result from the deficiency of a specific enzyme in the heme synthetic pathway. The clinical manifestations of the disease are determined by the accumulation of porphyrins and porphyrin precursors delta-aminolaevulinic acid and porphobilinogen. Porphyrias are generally divided into hepatic or erythropoietic types depending on the primary site of overproduction or accumulation of the precursors or porphyrins [4]. Porphyrias also can be classified as to whether or not they cause acute symptoms [3]. The latter classification is more useful to the anesthesiologist because anesthesia is known to be related to trigger acute porphyric reactions.

Postoperative AIP attack is unpredictable and rare in a previously undiagnosed patient. Various clinical presentations of AIP

can confound the diagnosis. Our patient did not have a previous diagnosis of porphyria, and no known family members had this disorder. This was her first experience of the anesthesia. She presented with delayed emergence from anesthesia and motor weakness. Firstly, the residual effect of general anesthetics or muscle relaxant is possible in a patient without a specific previous medical history, and so conservative management was maintained. Since the clinical signs showed no improvement after adequate recovery time, brain MRI was performed. The findings suggested WE. Thiamine deficiency can cause WE and a symmetric sensory-motor axonal polyneuropathy. Her recent oral intake was reduced because of perioperative fasting and preoperative abdominal pain, but she was not chronically malnourished. Although she was neither alcohol dependent nor malnourished, clinical manifestations were somewhat consistent with WE, so treatment with thiamine was started. In suspected patients, early and appropriate treatment should be given before disease confirmation. As intravenous administration of glucose can precipitate WE in thiamine-deficient patients [5], only intravenous thiamine was administered. Despite about 2 weeks of treatment, her neuropathic symptoms and neurophysiologic studies were not improved, and the patient did not present the characteristic symptoms of WE including ophthalmoplegia, nystagmus, ataxia and memory disturbance [5]. The neurologist reconsidered another form of peripheral neuropathy, GBS. GBS exhibits peripheral neuropathy with dysautonomia and GBS has also been reported following surgery [6]. Administration of intravenous immunoglobulin was ineffective and other symptoms including hyponatremia, seizure activity and aggravated respiratory muscle weakness developed. Subsequent test of urine and a series of presentations confirmed AIP. The patient expired due to cardiopulmonary complications of AIP caused by delayed diagnosis and management.

Clinical features of acute hepatic porphyrias include abdominal pain, vomiting, paralysis or weakness of limbs, hypertension, tachycardia, seizures and mental state changes [7]. Acute attacks of porphyria are most commonly precipitated by events that decrease heme concentrations and thus increase the activity of delta-aminolaevulinic acid synthetase and stimulate the production of porphyrinogens [1]. Activation of the disease is related to environmental and hormonal factors such as drugs, fasting, dehydration, surgery, menstruation, stress and infection [3]. Inadvertent drug use in undiagnosed porphyria patients may increase the severity of an acute attack. Enzyme-inducing drugs are the most important and frequent triggering factors in the development of acute porphyria, especially in relation to anesthesia. Many anesthetic drugs induce hepatic cytochromes are likely to trigger acute attacks [3,8]. The majority of reports on drug induced porphyric attack have concerned thiopental [2,3]. Although the drugs thought to be hazardous, such as thiopental,

etomidate and pentazocine, will not always precipitate a crisis, it would be safe to avoid these drugs in known porphyric patients [2,3]. There are many other drugs that are unlikely to prove safe or have too little evidence to reach a conclusion, and they should also be used with caution [2,3,9]. Perioperative starvation and dehydration can also trigger porphyric attack, and therefore preoperative fasting should be kept to a minimum. Carbohydrate loading can suppress porphyrin synthesis [8], dextrose containing fluid should be considered if starvation is prolonged.

The most common presenting finding of patients with AIP is severe abdominal pain. Other gastrointestinal symptoms include nausea, vomiting, diarrhea or constipation [4]. This patient presented abdominal pain with nausea and poor oral intake before the surgery, but the correlation of these symptoms and AIP is uncertain. Diagnostic workup on the pain was normal, and she recovered after treatment with 10% dextrose and routine gastrointestinal drugs. If her pain was due to mild acute porphyria attack, intravenous glucose infusion might be effective.

Neurologic manifestations may also develop including flaccid paralysis, seizures, neuropsychiatric disturbances and encephalopathy in 10 to 40% of acute attacks [10]. AIP presents with autonomic, peripheral neuropathy or central nervous system dysfunctions [7]. Clinical features of autonomic neuropathy are tachycardia, hypertension or postural hypotension; the patient displayed tachycardia and labile blood pressure during the postoperative period. Respiratory muscle weakness is common in untreated AIP. Axonal motor neuropathy is the characteristic electrophysiologic pattern of acute porphyric neuropathy [10,11]. Axonal forms of GBS may be similar to acute porphyric neuropathy in that it exhibits motor neuropathy with respiratory involvement, and autonomic neuropathy [6]. Our patient showed both upper and lower motor weakness combined with respiratory muscle weakness and dysautonomia without sensory loss. The diagnosis of AIP may be difficult from these neurologic findings without other typical signs because AIP is a rare differential diagnosis of acute motor axonal neuropathy. Hyponatremia, as seen in this case, is a common electrolyte abnormality in AIP, and can occur due to inappropriate antidiuretic hormone secretion or sodium loss via gastrointestinal or renal route [8]. Her epileptic activity on EEG may have been caused by hyponatremia or one of neurologic manifestations of AIP. The factors that correlate with a poor outcome include the extent of muscle weakness, mechanical ventilation, bulbar palsy, consciousness impairment and hyponatremia [12].

AIP was suspected belatedly because of the MRI findings. There are not typical neuroimaging findings of AIP. Most often reported MRI finding of AIP with severe encephalopathy is posterior reversible encephalopathy syndrome, which is evident as reversible symmetric regions of edema predominating in the occipital and parietal lobes in hypertensive patients, because

acute porphyric attacks are commonly associated with severe hypertension related to autonomic neuropathy [13]. Intraoperative hemodynamics of our patient was stable throughout the anesthesia, so her MRI finding did not hold a clue to the diagnosis of AIP.

Laboratory identification of porphyric attack involves measurement of urinary porphyrin and porphyrinogen precursors [1]. These are markedly increased during the attack, but may show normal during remission. This normality can make the diagnosis of latent porphyria patients difficult. Many carriers of the trait can remain asymptomatic until exposure to precipitants. Dover et al. [14] reported that the outcome in patients who were not diagnosed with porphyria at the time of surgery was extremely poor. The case fatality rate of an acute attack is low, unless a patient is misdiagnosed and additional precipitants are administered. Since the diagnostic test is simple, it would be good to perform in patients with unknown cause of motor axonal neuropathy.

Management of a porphyric crisis should include rapid recognition and elimination of any potentially porphyrinogenic drugs, adequate hydration and avoidance of low calorie diet or prolonged periods of fasting [8]. Patients with signs of respiratory insufficiency during an acute attack require immediate intubation and ventilation support. If initial treatment may not be effective, administration of heme is recommended because it suppresses endogenous heme synthesis and decreases significantly the excretion of delta-aminolaevulinic acid and porphobilinogen [2,8]. Early diagnosis, discontinuation of triggering factors and treatment can significantly reduce the mortality.

In conclusion, we present postoperative development of AIP with neurologic manifestations in an undiagnosed patient. The occurrence of delayed emergence and neurological disturbance in the recovery period is not simple to diagnose and AIP is a rare different diagnosis of these symptoms. Awareness of the features of this disease and the risk of undiagnosed cases is required to reduce associated morbidity and mortality.

References

1. Kauppinen R. Porphyrias. *Lancet* 2005; 365: 241-52.
2. Jensen NF, Fiddler DS, Striepe V. Anesthetic considerations in porphyrias. *Anesth Analg* 1995; 80: 591-9.
3. James MF, Hift RJ. Porphyrias. *Br J Anaesth* 2000; 85: 143-53.
4. Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment. *Blood* 2012; 120: 4496-504.
5. Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *Lancet Neurol* 2007; 6: 442-55.
6. Vucic S, Kiernan MC, Cornblath DR. Guillain-Barre syndrome: an update. *J Clin Neurosci* 2009; 16: 733-41.
7. Simon NG, Herkes GK. The neurologic manifestations of the acute porphyrias. *J Clin Neurosci* 2011; 18: 1147-53.
8. Kalman DR, Bonkovsky HL. Management of acute attacks in the porphyrias. *Clin Dermatol* 1998; 16: 299-306.
9. Gorchein A. Drug treatment in acute porphyria. *Br J Clin Pharmacol* 1997; 44: 427-34.
10. Kuo HC, Huang CC, Chu CC, Lee MJ, Chuang WL, Wu CL, et al. Neurological complications of acute intermittent porphyria. *Eur Neurol* 2011; 66: 247-52.
11. Andersson C, Nilsson A, Bäckström T. Atypical attack of acute intermittent porphyria--paresis but no abdominal pain. *J Intern Med* 2002; 252: 265-70.
12. Pischik E, Bulyanitsa A, Kazakov V, Kauppinen R. Clinical features predictive of a poor prognosis in acute porphyria. *J Neurol* 2004; 251: 1538-41.
13. Utz N, Kinkel B, Hedde JP, Bewermeyer H. MR imaging of acute intermittent porphyria mimicking reversible posterior leukoencephalopathy syndrome. *Neuroradiology* 2001; 43: 1059-62.
14. Dover SB, Plenderleith L, Moore MR, McColl KE. Safety of general anaesthesia and surgery in acute hepatic porphyria. *Gut* 1994; 35: 1112-5.