Case Report

Lactic Acidosis Associated with Severe Neuromuscular Weakness and Stavudine Therapy†

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Nucleoside analogue reverse-transcriptase inhibitors (NRTIs) especially stavudine, used for the treatment of HIV infection have been rarely associated with lactic acidosis syndrome (LAS) and severe neuromuscular weakness mimicking Guillain Barre syndrome. A 36-year-old man presented with a one-week history of nausea, vomiting, epigastric pain, dyspnea associated with progressive muscle weakness and numbness in glove and stocking pattern. He had symptomatic HIV infection, diagnosed 2 years before the admission and was treated with GPOvir (lamivudine, stavudine and nevirapine). Physical examination revealed afebrile dyspnic drowsy man with crepitation in both lungs and hepatomegaly. Neurological examination showed areflexic symmetrical weakness of both extremities and decreased pin-prick sensation in glove and stocking pattern as well as loss of vibration and touch sensation in both hands and feet. He developed cardiopulmonary arrest and was intubated. Investigations revealed severe lactic acidosis (lactic acid = 21.1 mg/dl). Electrophysiological studies revealed severe sensorimotor axonopathy predominantly involved the lower extremities. Stavudine was discontinued. Severe LAS dramatically improved and polyneuropathy gradually recovered with symptomatic as well as supportive interventions. Monitoring of LAS and neuromuscular weakness is advocated in HIV patient who receive stavudine therapy. Immediate discontinuation of the medication after detection of these complications may prevent this fatal complications.

Keywords: *Lactic acidosis syndrome, Neuromuscular weakness, Guillain Barre syndrome, Stavudine*

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Nucleoside analogue reverse-transcriptase inhibitors (NRTIs), are often used in combination with other antiretroviral drugs as highly active antiretroviral therapy (HAART). Chronic compensated asymptomatic hyperlactatemia is common with NRTIs usage[1]. However, severe adverse drug reactions, especially lactic acidosis and rapidly ascending neuromuscular weakness are rarely reported[2-4]. The present complication may be progressive and result in respiratory failure. Prompt diagnosis and appropriate management of this fatal syndrome is crucial[2-4]. The authors describe a Thai patient with HIV associated lactic acidosis syndrome (LAS) and severe neuromuscular weakness mimicking Guillain Barre' syndrome. The syndrome dramatically improved after the discontinuation of stavudine. The recognition of this unique syndrome is very important in the era of antiretroviral therapy

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Case Report

A 36-year-old man was followed-up for symptomatic HIV infection since May 2007. At that time, he presented with two-month history of cough, fatigue, anorexia, significant weight loss. He was an intravenous drug user and had multiple partners. Physical examination revealed oral candidiasis, multiple cervical lymphadenopathy, needle marks and pruritic papular eruption. Chest x-ray showed reticulonodular infiltration at left upper lung with left pleural effusion. Serology for HIV infection was positive with CD4 cell count of 75/mm^3 (11%), viral load of 145,000 copies per mm^3. Sputum AFB was negative and anti-HCV was positive. He was treated with a 6-month course of anitituberculous drugs and co-trimoxazole. He strictly complied with GPOvir S30 (stavudine 30 mg, lamivudine 150 mg and nevirapine 300 mg) twice a day. CD4 cell count was 107/mm^3 (8%) and 157/mm^3 (13%) at 6 and 11 months after starting this regimen while the viral

load was less than 50 copies per mm^3 at 11 months after the treatment.

In July 2008, he presented with a two-week history of progressive extremity numbness in glove and stocking pattern. He developed progressive proximal weakness of the lower extremities 2 day after the numbness. He could not walk by himself two days before the admission. He also had progressive dyspnea, epigastric pain, nausea, vomiting and oliguria. Physical examination revealed afebrile drowsy man with dyspnea, tachypnea and tachycardia. He had coarse crepitation, wheezing and hepatomegaly. Neurological examination revealed areflexic symmetrical proximal weakness of both extremities. He also had decreased pin-prick sensation in glove and stocking pattern and loss of vibration and touch sensation in both hands and feet.

Laboratory revealed: hemoglobin 13.6 g/dl, white blood cell 9,230 /mm^3 with 72% polymorphonuclear cell, 19.7% lymphocyte, 7.5% mononuclear cell, platelet 332,000 /mm^3, plasma glucose 450 mg/dl, BUN 51 mg/dl, creatinine 8.9 mg/dl, globulin 3.4 mg/dl, albumin 5.1 mg/dl, total bilirubin 0.60 mg/dl, direct bilirubin 0.14 mg/dl, SGOT 93 U/L, SGPT 144 U/L, alkaline phosphatase 142 U/L, amylase 50 U/L, sodium 135 mmol/L, potassium 5.9 mmol/L, chloride 95 mmol/L, bicarbonate 4 mmol/L, anion gap 36 mmol/L, lactic acid 21.1 mg/dl, pH 6.921, pCO_2 18.8 mmHg, pO_2 73.4 mmHg, and bicarbonate 3.8 mmol/L (with oxygen mask with bag 10 L/min). Chest x-ray revealed bilateral puImonary congestion.

LAS and neuromuscular weakness syndrome associated with stavudine therapy was diagnosed. He developed cardiopulmonary arrest. After resuscitation, he was intubated and hemodynamic status was maintained by inotropic drugs. Lactic acidosis and hyperglycemia were treated with sodium bicarbonate and insulin infusion. Hemodialysis and supportive ventilator were started due to acute renal failure, respiratory failure and severe lactic acidosis. Antiretroviral therapy was stopped. The hemodynamic status improved after continuing hemodialysis and supportive ventilator for 4 days. The inotropic drugs were tapered and hemodialysis as well as supportive ventilator were discontinued on the fourth day of admission. However his numbness and lower extremities weakness persisted. Lumbar puncture was performed on the fifth day after the admission and revealed acellular CSF with protein of 41.2 mg/dl, CSF glucose/plasma glucose of 62/117 mg/dl. CSF culture and serology test for bacteria, fungus and herpes virus revealed negative result. Six weeks after the admission, electrophysiologic studies were performed and revealed evidences of sensorimotor axonopathy predominantly involved the lower extremities.

His weakness was gradually improved within one month and he could walk with gait aid. The improvement of numbness was much more slower. On discharge, stavudine was replaced by another antiretroviral regimen (tenofovir, lamivudine and efavirnz). After 9 month of follow-up, he had no weakness and deep tendon reflexes were 1+ in all extremities but minimal numbness of the lower extremities were still detected.

Discussion

LAS is often associated with symptoms of generalized fatigue, anorexia, nausea, vomiting, abdominal pain, abdominal distension and hepatomegaly[5]. Tachypnea, dyspnea and acute respiratory failure signals a preterminal state of LAS[5]. Serum transaminase levels often rise in patients with LAS[5]. An elevated plasma lactate level more than 2 mmol/L in combination with wide anion gap acidosis in the absence of other causes of metabolic acidosis is diagnostic for LAS[5,6]. Stavudine is the most common cause of NRTIs associated lactic acidosis[7]. Apart from prolonged dideoxynucleosides exposure especially stavudine, other risk factors for hyperlactacemia/ LAS in HIV infected patient included, advanced immunosuppression, pregnancy and female gender[7]. This advanced HIV patient received stavudine for almost one year and developed LAS. He also had severe neuromuscular weakness and respiratory failure. Lactic acidosis associated with rapidly ascending neuromuscular weakness usually occur within 4-5 weeks of each other[2-4]. Severe neuromuscular weakness associated with lactic acidosis in HIV infected patients has been classified as: possible (progressive weakness due to neuromuscular disease), probable (progressive weakness with exclusion of other causes), definite (progressive weakness with electrophysiological or pathological evidence of neuromuscular lesion)[2]. The clinical syndrome which may mimic Guillain Barre syndrome includes: numbness, dysesthesia, paresthesia, areflexic limb weakness, facial and bulbar weakness, ophthalmoparesis, ptosis and nystagmus[2]. Miller Fisher variant of Guillain Barre syndrome associated with lactic acidosis and stavudine therapy has also been reported[8]. According to the clinical profiles, laboratory tests including CSF analysis and electrophysiological

studies, this patient could be classified as definite HIV-associated neuromuscular weakness and LAS[2]. Electrophysiologic studies revealed evidences of sensorimotor axonopathy, predominantly involved the lower extremities. Prompt discontinuation of stavudine and appropriate symptomatic as well as supportive cares, dramatically improved LAS. His polyneuropathy also had a nearly complete recovery course after 9 month follow-up without specific treatment.

The NRTIs inhibit HIV replication due to their high affinity for viral enzyme reverse transcriptase[9]. However, NRTIs can also bind to human DNA polymerase and cause many adverse drug reactions[9]. NRTIs bind to mitochondrial DNA polymerase gamma and promote mitochondrial dysfunction, resulting failure of glucose metabolism, energy production and increas production of lactate[9]. Stavudine, one of dideoxynucleosides (stavudine, didanosine and zalcitabine), was particularly associated with a decreased in mitochondrial DNA due to its high ability to enter cell and transport to mitochondrial membrane[10]. Stavudine has been associated with the development of lactic acidosis/hyperlactataemia[11] and neuromuscular weakness syndrome[2]. The acute neuromuscular weakness syndrome may mimic Guillain Barre or Miller-Fisher syndrome[2-4,8]. Electrophysiological findings documented neuropathy as well as myopathy or mixed neuromyopathy[2]. Sensorimotor polyneuropathy may be axonopathy, demyelinating process or mixed[2]. Pathological studies paralleled electrophysiological findings[2]. Moreover, inflammatory process involving nerves as well as muscles have been encountered in some cases[2]. Usually, neuromuscular weakness syndrome occurs in the course of lactic acidosis and the cause of the syndrome is presumed to be related to mitochondrial dysfunction[2]. However, in some cases, there may be a delay from time of lactic acidosis presentation, and consequent dideoxynucleosides withdrawal, to the onset of neuromuscular syndrome[12,13]. The delayed neuromuscular manifestation was postulated to be related to the recovery in mitochondrial function after dideoxynucleosides discontinuation[12,13]. The recovery in mitochondrial function may further promote immunological mechanism and cause inflammatory reaction demonstrated in nerve and muscle[2]. Treatment of severe neuromuscular weakness syndrome associated with lactic acidosis in HIV-infected patients are inconclusive. Apart from symptomatic and supportive cares, other reported interventions included: intravenous immunoglobulin, plasmapheresis, corticosteroids, coenzyme Q10, carnitine, acetylcarnitine, vitamin B1, B12[2]. This syndrome has 20% mortality rate[2]. The neuromuscular syndrome usually improve within two month to one and a half year but the degree of recovery may vary[2]. In the contex of prevention of lactic acidosis/hyperlactatemia and neuromuscular weakness syndrome, patient should be warned about the possibility of potentially lethal complication of dideoxynucleosides therapy. Early clinical syndrome of lactic acidosis and motor weakness should be recognized and immediate discontinuation of the medication is advocated. However, routine monitoring of serum lactate level in asymptomatic patient is not recommended[14].

In conclusion, LAS and severe neuromuscular weakness syndrome may occur in HIV-infected patient with NRTI exposure. Early recognition of LAS and neuromuscular syndrome is crucial. Prompt discontinuation of the causative NRTIs may prevent fatal complication of this syndrome.

Potential conflicts of interest

None.

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ภาวะแลคติกอะซิโดสิสและอาการอ่อนแรงของกล้ามเนื้ออย่างรุนแรง และการรักษาด้วยยาสตาร์วูดีน

พงศ์ภัทร์ วรสายัณห์, กัมมันต์ พันธุมจินดา

ยา nucleoside analogue reverse-transcriptase inhibitors (NRTI) โดยเฉพาะสตาวูดีนที่ใช้ในการรักษาการติดเชื้อเอชไอวี มีความสัมพันธ์กับการเกิดกลุ่มอาการแลคติกอะซิโดสิส และอาการกล้ามเนื้ออ่อนแรงอย่างรุนแรง ซึ่งให้ลักษณะคล้ายกลุ่มอาการกีแลงแบร์ แต่พบได้น้อย ผู้ป่วยชายอายุ 36 ปี มาด้วยประวัติ อาการคลื่นไส้ อาเจียน ปวดบริเวณเหนือกระเพาะอาหาร หายใจลำบากร่วมกับอาการอ่อนแรงของกล้ามเนื้อ และอาการชาแบบสวมถุงมือถุงเท้า ที่เป็นมากขึ้นภายในระยะเวลาหนึ่งสัปดาห์ ผู้ป่วยมีการติดเชื้อเอชไอวีที่แสดงอาการซึ่งได้รับการวินิจฉัย 2 ปี ก่อนเข้าโรงพยาบาลครั้งนี้ และได้รับการรักษาด้วยจีพีโอเวียร์ (ลามิวูดีน, สตาวูดีน และเนอร์วิราปีน) การตรวจร่างกายพบ ผู้ป่วยชายไม่มีไข้ หอบเหนื่อย ซึม และพบเสียงกรอบแกรบในปอด 2 ข้าง ร่วมกับตับโต การตรวจร่างกายทางระบบประสาท พบอาการอ่อนแรงที่สมมาตรของแขนขาทั้ง 2 ข้าง โดยตรวจไม่พบรีเฟล็กซ์ พบการลดลงของความรู้สึกเจ็บปวดในลักษณะสวมถุงมือและถุงเท้าร่วมกับการสูญเสียความรู้สึกสั่นสะเทือน และการสัมผัสที่มือและเท้าทั้ง 2 ข้าง ผู้ป่วยเกิดภาวะหัวใจและการหายใจล้มเหลว และต้องใส่ท่อช่วยหายใจ การตรวจทางห้องปฏิบัติการพบภาวะกรดแลคติกสูงรุนแรง (กรดแลคติกเท่ากับ 21.1 มิลลิกรัม/เดซิลิตร) การตรวจทางประสาทสรีรวิทยาพบโรคในระบบประสาทส่วนปลาย ที่เป็นกับปลายประสาททั้งส่วนของระบบประสาทรับความรู้สึก และระบบประสาทสั่งการชนิดแอกซอน ซึ่งพบเด่นบริเวณขาทั้งสองข้าง สตาวูดีน ได้รับการถอนออกจากการรักษากลุ่มอาการแลคติกอะซิโดสิส ที่เป็นอย่างรุนแรงดีขึ้นอย่างชัดเจน และโรคระบบประสาทส่วนปลายค่อย ๆ ฟื้นตัวโดยการรักษาตามอาการร่วมกับการรักษาแบบประคับประคองในผู้ป่วยติดเชื้อเอชไอวี ที่ได้รับการรักษาด้วย สตาวูดีน ควรได้รับการประเมินกลุ่มอาการแลคติกอะซิโดสิส และอาการอ่อนแรงของกล้ามเนื้อในระหว่างการรักษา เมื่อเกิดภาวะดังกล่าวทั้งสองขึ้นการหยุดยาทันทีอาจป้องกันภาวะแทรกซ้อน ซึ่งอาจทำให้ถึงแก่ชีวิตชนิดนี้ได้