J Korean Med Sci 1998; 13: 449-53
ISSN 1011-8934

Acute Transverse Myelitis caused by Coxsackie Virus B4 Infection : A Case Report

Acute transverse myelitis is a rare clinical manifestation of Coxsackie virus infection which cause acute and progressive debilitating illnesss associated with loss of spinal cord function in the affected patients. A 62 year-old female developed symptoms of rapidly progressive paraplegia with sensory loss. On spinal MRI, T2 sagittal image showed increased signal intensity with cord swelling at T11-L2 level and 8 folds or greater rise of Coxsackie virus B4 neutralizing antibody titers was observed in the CSF. There is only one previous report of acute transverse myelitis caused by Coxsackie virus B4 infection to our knowledge. The presence of specific viral antibody titers change in the CSF and a corresponding spinal cord lesion are sufficient to suggest a causal relationship between the virus and the illness. This article is a case report of an unusual acute transverse myelitis caused by Coxsackie virus B4 infection.

Key Words : *Myelitis transeverse; Coxsackievirus B; Antigen-antibody reactions*

Bondae Ku, Kayhoon Lee

Department of Neurology, Pochon CHA University College of Medicine, Kyonggi, Korea

Received : September 27, 1997
Accepted : March 31, 1998

Address for correspondence
Bondae Ku, M.D.
Department of Neurology, Kyung-Hee Pundang CHA General Hospital, 351 Yatap-dong, Pundang-gu, Sungnam, Kyonggi 463-070, Korea
Tel : +82.342-780-6066, Fax : +82.342-780-6066
E-mail : merritt@hitel.net

INTRODUCTION

Transverse myelitis is a well recognized clinical illness, characterized by abrupt onset of progressive weakness in the limbs, sensory impairment and loss of the rectal and the bladder sphincter tone (1). Various infectious agents have been described as the cause of transverse myelitis and about 20% to 40% of causes of the illness are attributed to viral infection although a specific virus is rarly identified (1, 2). Among the viruses causing transverse myelitis, the most important one is the Enterovirus (3). Enterovirus, especially Coxsackie virus A7, A9 and A23 (Echovirus 9) and Coxsackie virus B strains frequently cause meningo-encephalitis often associated with transient or permanent paralysis (3, 4). There is a report of a 10 year-old girl with transverse myelitis who had demonstrated a rise of Coxsackie virus B4 neutralizing antibody titers and this is the only previous report of acute transverse myelitis caused by Coxsackie virus B4 infection to our knowledge (5). We now describe an unususal acute transverse myelitis caused by Coxsackie virus B4 infection developed in a 62 year-old female confirmed by the rise of the neutralizing antibody titers in the CSF and spinal cord lesion on MRI imaging.

CASE DESCRIPTION

A 62 year-old right-handed female visited the emergency medical center because of weakness at both lower extremities. At that morning, she had suffered low back pain and a tight sensation in both posterior thighs and 8 hours later, she had experienced progressive ascending weakness of both lower extremities accompanied with sensory impairment. 10 hours after the onset of symptoms, she had been unable to stand. There were no history of toxin exposure or ingestion, trauma, insect bite and recent vaccination but she had experienced mild flu-like symptoms such as fever, general myalgia etc, before 1 week the onset of symptoms.

On physical examination, blood pressure was 130/80 mmHg, pulse rate 72/min, body temperature 36.3℃, and respiration rate 20/min. There were no skin rashes and cervical lymph nodes enlargement.

On neurologic examination, her consciousness was clear and oriented. Cranial nerves showed no abnormality. Complete motor paralysis in the right leg and trace degree of weakness in the left leg accompanied with flaccid muscle tone were noted but the muscle bulk was not atrophied. Deep tendon reflexes were decreased in both lower extremities. No plantar responses or clonic movements were noted in both lower extermities. Meningeal irritation signs including nuchal rigidity were not detected. Sensation was decreased in all modalities below the level of L3 on the right side and L1 on the left side. Anal sphincter tone was reduced and urinary retention was present.

The peripheral blood study and serum chemistry were

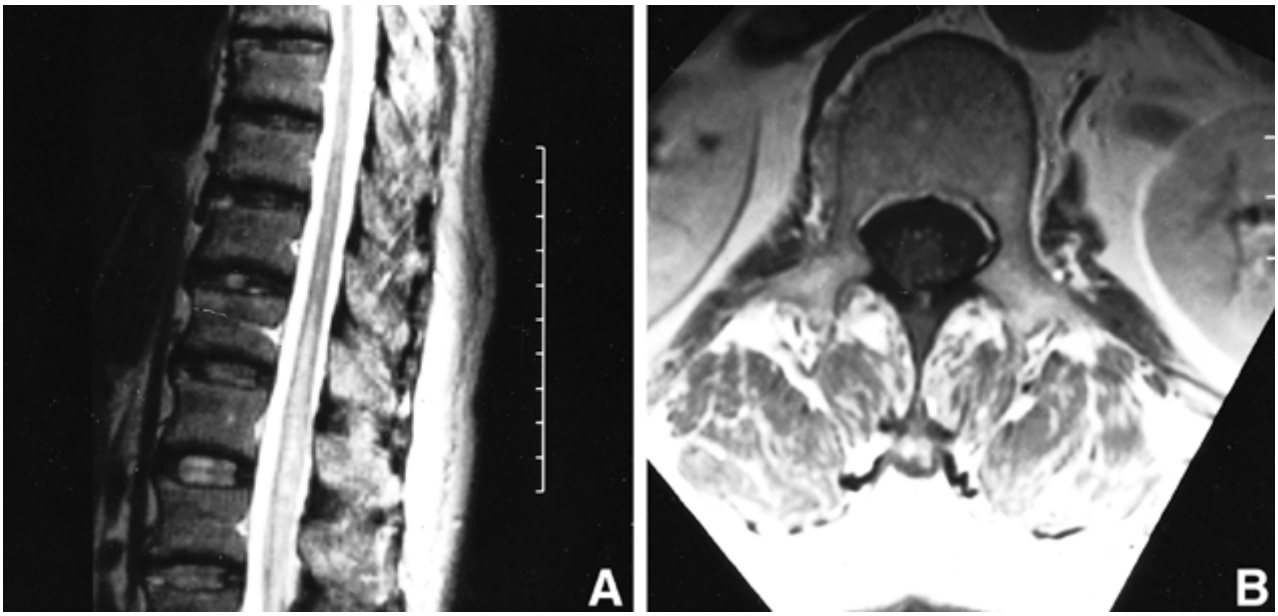

Fig. 1. Spinal MRI. (A) T2-weighted sagittal image shows linear high signal intensity with mild cord swelling in T11-L2 level. (B) T1-weighted axial enhanced image at the level of L1 shows that, the lesion involves mainly gray matter showing no significant enhancement.

within reference values. Chest and spinal column radiography were unremarkable.

The CSF study was done on admission day. The findings were as follows: color was clear, opening pressure 150 mmHg, white blood cell 0/mm^3, red blood cell 1/mm^3, protein 63 mg/dL, glucose 79 mg/dL, chloride 126 mEq/dL.

Spinal MRI on 2nd hospital day showed high signal intensity with mild cord swelling at T11-L2 level in sagittal T2 image and in enhanced T1 axial image, the lesion involved mainly gray matter showing no significant enhancement. On enhanced T1 sagittal image, no foci of high velocity signal loss in epidural space were detected that can be seen in arteriovenous malformation or infarction of the spinal cord (Fig. 1).

The next day, she had complete paraplegia and sensory loss below L1 level in all modalities.

The second CSF study was done 11th hospital day. The findings were: color was clear, opening pressure 85 mmHg, white blood cell 6/mm^3, red blood cell 2/mm^3, protein 107 mg/dL, glucose 63 mg/dL, chloride 123 mEq/dL. No bacteria and fungus were seen in direct smear and a culture subsequently proved negative. The titers of CMV-IgM, EBV(VCA)-IgM, Varicella zoster IgM, Herpes IgM were negative. Neutralizing antibody titers in Poliovirus, Coxsackievirus and Echovirus strains showed an eight-folds increases in Coxsackie virus B type 4.

The third CSF study was done 46th hospital day. The findings were: color was clear, opening pressure 60 mmHg, white blood cell 1/mm^3, red blood cell 0/mm^3, protein 43 mg/dL, glucose 69 mg/dL, chloride 116 mEq/ dL. The neutralizing antibody to Coxsackie virus showed all below 1:1 including Coxsackie virus B type 4 (Fig. 2).

The patient was managed with intravenous dexamethasone followed by a reducing dose of oral prednisolone was given immediately on admission. But in spite of steroid therapy, she had persistent complete paraplegia with sensory loss below L1 level.

Follow up spinal MRI on 51th hospital day showed unchanged high signal intensity at T11-L2 level in sagittal T2 image and on enhanced T1 axial image, the lesion still involved mainly gray matter showing no sig-

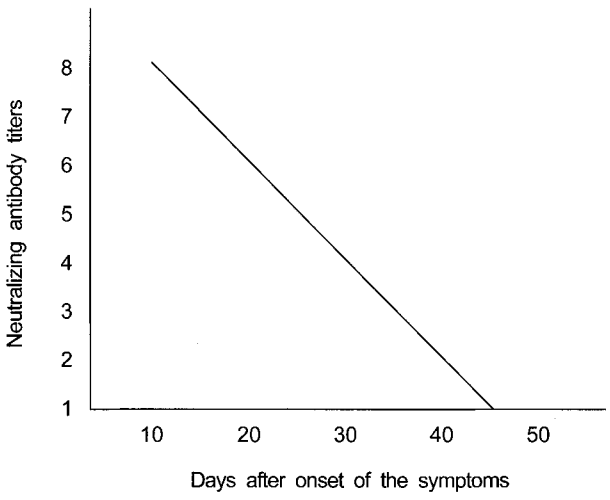

Fig. 2. Neutralizing antibody titers change in the CSF.

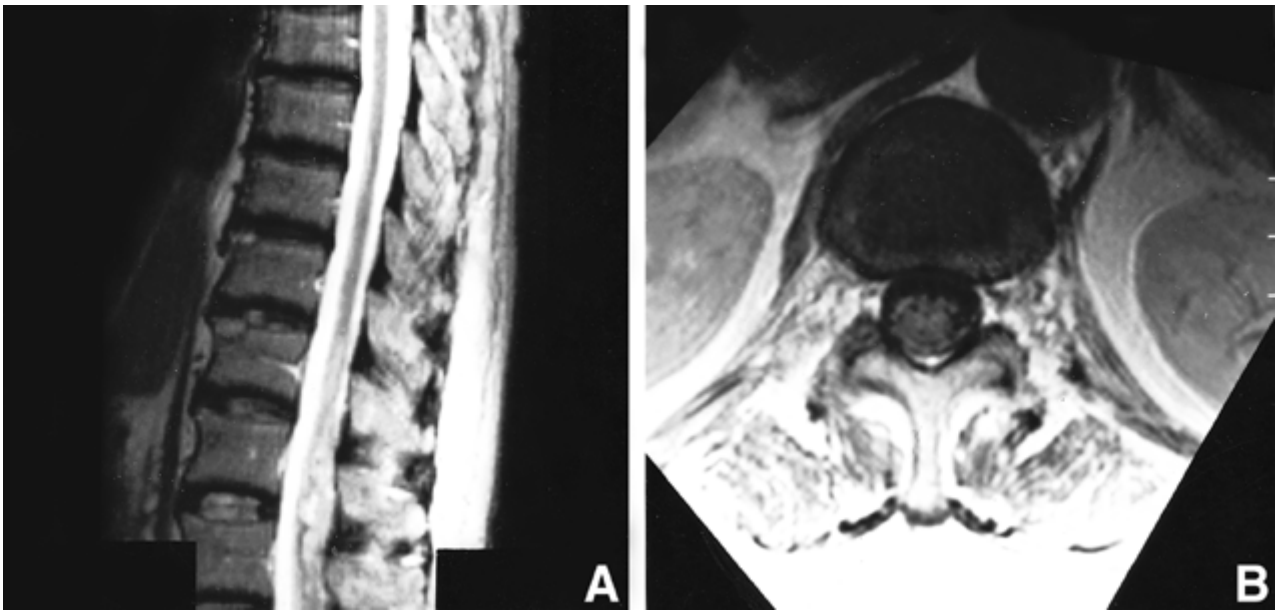

Fig. 3. Follow up spinal MRI. (A) T2-weighted sagittal image shows unchanged linear high signal intensity in T11-L2. (B) enhanced T1 axial imageat the level of L1, the lesion still involved mainly gray matter showing no significant enhancement accompained with marked back muscle atrophy.

nificant enhancement accompanied with marked back muscle atrophy (Fig. 3).

After 71 days of hopitalization she discharged with persistent flaccid areflexic paraplegia without recovery of motor, sensory, and sphincter tone.

DISCUSSION

Although the etiology of transverse myelitis is various and may be idiopathic, occasionally it may occur in association with viral infection (6). Several viruses including measles, rubella, Ebstein Barr virus, varicella zoster virus, cytomegalovirus, herpes simplex virus, Echo virus, mumps, hepatitis and Coxsackie virus are the well known viral agents (1, 2, 7, 8, 9, 10, 11).

Coxsackie virus was identified first from the specimens collected in the village of Coxsackie on the banks of the Hudson river, but it was soon found to be world-wide in distribution (4).

Coxsackie viruses are accepted as the cause of benign aseptic meningitis, encephalitis, Guillian-Barre syndrome and mild poliomyelitic syndrome but in comparison with poliomyelitis, transverse myelitis has been rarely described in association with Coxsackie virus (5, 7, 12). Especially the group of Coxsackie virus A type 5 and 9 are well known organisms of acute central nervous system infection (7).

The infectivity of Coxsackie virus is due to its ribonucleic acid, and the protein coat has antigenicity but neutralizing antibody is ineffective against viral ribonucleic acid which in turn is rapidly destroyed by ribonuclease (4).

There has been a few previous reports of transverse myelitis due to Coxsackie virus infection (5, 7, 9, 12). Graber et al. reported acute transverse myelitis and Coxsackie virus A9 infection (7). Jarcho et al. reported encephalitis and poliomyelitis due to Coxsackie virus B5 (12), Matthews et al. reported transverse myelitis associated with Coxsackie B3 infection (9) but there was only one previous report of transverse myelitis due to Coxsackie virus B4 infection by Dery et al. to the best of our knowledge (5). Our patient is similar to the patient of Dery et al. in that both low extremities weakness and a rising of Coxsackie virus B4 neutralizing antibody titer but is differentiated from their patient by the following points: 1) Our patient has been flaccid areflexic paraplegia with complete sensory loss while their patient has been increased muscle tone, bilateral Babinski signs and partially preserved sensation, 2) Our patient showed normal initial CSF study but their patient showed lymphocyte predominant pleocytosis in initial CSF study, 3) Our patient have showed no improvement of weakness but their patient had recovered 4 days after onset of symptoms, 4) Our patient demonstrated spinal cord signal change in MRI but their patient did not.

In some types of viral infection, myelitis is only a part of more global CNS infection (2). In some viral infection, the development of neurological complications may be due to systemic viremia, virus reactivation, and delayed

type hypersensitivity (13, 14). There were two case reports of acute myelitis after hepatitis B vaccination and recurrent herpes zoster myelitis (10, 11).

The subsequent viremia following the incubation period, usually 2-7 days, accounts for the biphasic character of many clinical Coxsackie syndromes and their multiorgan involvement (4).

At present, three hypotheses have been proposed to explain the pathogenesis of transverse myelitis: cell mediated, post-infectious, autoimmune response; direct invasion of pathogens in the spinal cord; and acute vascular occlusion (1, 10). Sometimes, it may be difficult or impossible to distinguish between post-infectious immune mediated tissue injury and direct viral invasion, but the presence of specific virus in CSF is compatible with a direct viral involvement of the spinal cord (1, 7). Some reported pathologic studies suggest that the myelopathy was due to both direct viral invasion of the spinal cord and virus induced vasculitis (2, 14). Pathologically, perivenous lymphocytic infiltration with area of demyelination and associated microglial reaction are observed which may result in superimposed ischemia and arterial spasm (15). At necropsy case, necrotising arteritis of the anterior spinal artery and cystic myelomalacia of the spinal cord were observed (2).

Transverse myelitis is a neurologic condition that presents with bilateral limb weakness and sensory loss associated with bowel and bladder dysfunction (2, 6). Although signs such as nystagmus, facial palsy, sixth nerve palsy, brisk jaw jerk may be present, the illness is limited primarily to the spinal cord (3). Persistent urinary incontinence resulted in detrusor-external sphincter dyssynergia including detrusor hyperflexia, and sometimes erectile or ejecuratory dysfunction were reported (16).

An increasing of the specific antibody titers in the CSF have two possibilities: the product of diffusion or active transport from serum, and local production of antibody in the central nervous system (17, 18). It is well known that in certain neurologic conditions, the ratio of globulin to albumin in the CSF is reserved, the normal value being 1:4, and in central nervous system infection, the CSF containes γ globulin produced in the nervous system and a rise of γ globulin is associated with a raised lymphocyte count in the CSF (17). There was also an animal experimental report that neutralizing antibody production to Coxsackie virus B1, peaked 6-8 days after infection and was probably IgM immunglobulin (18). An increased CSF : serum ratio of neutralizing antibody titers can be used as a serological test for diagnosis and another serological testing performed by comparing titers in acute and convalescent samples with a four-fold or greater rise in antibody titers may also be diagnostic (5, 17, 19). Certain viral infections of the central nervous system can be diagnosed by demonstrating intrathecal synthesis of specific antibody and a high titer of a specific viral antibody in the CSF is suggestive evidence of central nervous system infection with a proposal strong etiological relationship between the virus and the patients condition (3, 20).

Although the biopsy is an invasive procedure, isolation of the virus from biopsy specimens offers a definite diagnosis (12, 13). Coxsackie virus can be isolated from the CSF in about half of the cases and is of obvious diagnostic values (21).

A myelogram or equivalent diagnostic procedure should be performed to exclude extra-medullary disorders (2). However the diagnosis of intramedullary disorder is difficult to be confirmed by conventional radiologic investigations thus the MRI imaging may be considered the best diagnostic modality in the intramedullary space (14, 22). Common MRI findings of transverse myelitis are fusiform swelling of the cord having increased signal intensity with occasional gadolinium enhancement in T2 weighted sagittal scan and centrally located hyperintensity of the cross-sectional area of the cord with variable enhancement pattern in T2 weighted axial scan (1, 23).

Long-term follow-up may show atrophy with increased signal intensity on T2 weighted sequence consistent with myelomalacia and gliosis (15). Existence of atrophy and remaining high signal intensity in follow up MRI have suggested a poor prognosis (1).

There is no specific treatment for patients with acute transverse myelitis but corticosteroids have been used for acute stage of myelitis but their efficacy are controversal (6, 24).

The time for partial or complete recovery of motor and sensory function may be several months (6). About one-third of the patients with transverse myelitis shows a good recovery, in another one-third, recovery is only partial and others fail to improve or die (25). The poor prognostic factors of transverse myelitis include severe limb weakness, wide spread abnormal MRI change, and unrecordable electrophysiologic studies (26). Prolonged bladder or sexual dysfunction may persist despite a systemic neurologic recovery (16).

We think that the 8-folds or greater neutralizing antibody titers change in the CSF and corresponding spinal cord lesion may be sufficient to suggest a causal relationship of the illness and virus in this case.

REFERENCES

1. Takahashi S, Miyamoto A, Oki J, Azuma H, Okuno A. *Acute transverse myelitis caused by ECHO virus type 18 infection. Eur J Pediatr 1995; 154: 378-80.*

2. Kenneth LT, Robert AG, Gregory DC. *Unusual viral causes of transverse myelitis: Hepatitis A virus and cytomegalovirus. Neurology 1986; 36: 855-8.*
3. Gear JHS. *Non-polio causes of polio-like paralytic syndrome. Rev Infect Dis 1984; 6(suppl 2): 379-84.*
4. Lerner AM, Finland M. *Coxsackie viral infections. Arch Intern Med 1961; 108: 329-34.*
5. Dery P, Mark MI, Shapera R. *Clinical manifestation of Coxsackie virus infection in children. Am J Dis Child 1974; 128: 464-8.*
6. Kelly CE, Mathews J, Noskin GA. *Acute transverse myelitis in emergency department: a case report and review of the literature. J Emerg Med 1991; 9: 417-20.*
7. Graber D, Fossoud C, Crauteau E, Gayet-Mengelle C, Carriere J-P. *Acute transverse myelitis and coxsackie A9 virus infection. Pediatr Infect Dis J 1994; 13: 77.*
8. Barak Y, Schwarz JF. *Acute transverse myelitis associated with ECHO type 5 infection. Am J Dis Child 1988; 142: 128.*
9. Matthews TG, Bailey SC. *Transverse myelitis -association with coxsackie B_3 infection? Arch Dis Child 1977; 52: 518-9.*
10. Song KS, Kim HC, Yun YH. *Acute myelitis after hepatitis B vaccination. J Korean Med Sci 1997; 12: 249-51.*
11. Baik JS, Kim WC, Heo JH, Zhang HY. *Recurrent herpes zoster myelitis. J Korean Med Sci 1997; 12: 360-3.*
12. Jarcho LW, Fred HL, Castle CH. *Encephalitis and poliomyelitis due to coxsackie virus group B type 5. N Engl J Med 1963; 268: 235-8.*
13. Shyu W-C, Lin J-C, Harn H-J, Lee C-C, Tsao W-L. *Recurrent ascending myelitis: an unusual presentation of herpes simplex virus type I infection. Ann Neurol 1993; 34: 625-37.*
14. Heller HM, Carnevale NT, Steigbigel RT. *Varicella zoster virus transverse myelitis without cutaneous rash. Am J Med 1990; 88: 550-1.*
15. Tartaglino LM, Flander AE, Rapport RJ. *Intramedullary causes of myelopathy. Semin Ultrasound CT MRI 1994; 15: 158-88.*
16. Berger Y, Blavis JG, Oliver L. *Urinary dysfunction in transverse myelitis. J Urol 1990; 144: 103-5.*
17. Lipton MM, Stiegman AJ, Dizon FC. *Poliovirus neutralizing antibody in cerebrospinal fluid. J Infect Dis 1965; 115: 356-62.*
18. William HB, Lloyd CB, Abner LN. *Thymus dependence of viral antigens. Nature 1975; 256: 654-6.*
19. Tapani H, Mirua S, Esko K. *Diagnosis of poliomyelitis by demonstration of intrathecal synthesis of neutralizing antibodies. J Infect Dis 1986; 153: 998-9.*
20. Dykers TI, Brown KL, Gundersen CB, Beaty BJ. *Rapid diagnosis of LaCrosse encephalitis: detection of specific immunoglobulin M in cerebrospinal fluid. J Clin Microbiol 1985; 22: 740-4.*
21. Wenner HA. *The enteroviruses: Recent advances. Yale J Biol Med 1982; 55: 185-203.*
22. Awerbuch G, Feinberg WM, Ferry P, Komar NN, Clements J. *Demonstration of acute post-viral myelitis with magnetic resonance imaging. Pediatr Neurol 1987; 3: 367-9.*
23. Choi KH, Lee KS, Chung SO, Park JM, Kim YJ, Kim HS, Shinn KS. *Idiopathic transverse myelitis: MR characteristics. Am J Neuroradiol 1996; 6: 1151-60.*
24. Sebire G, Hollenberg H, Meyer L, Huault G, Landrieu P, Tardieu M. *High dose methylprednisolone in severe acute transverse myelopathy. Arch Dis Child 1997; 76: 167-8.*
25. Berman M, Feldman S, Alter M, Zilber N, Kahana E. *Acute transverse myelitis: incidence and etiologic consideration. Neurology 1981; 31: 966-71.*
26. al Deeb SM, Yaqub BA, Bruyn GW, Biary NM. *Acute transverse myelitis: a localized form of postinfectious encephalomyelitis. Brain 1997; 120: 5-22.*