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Parkinsonism with long term use of lamivudine

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Abstract

This is a report of 3 cases of parkinsonism with long term administration of lamivudine. The clinic features were mask like faces, shuffling gait, lethargy and reduced automatic movement. After stopping use of lamivudine and treatment of anticholingeric drugs, the symptoms and signs of all cases were ameliorated. The possibilities of Wilson's disease and other secondary parkinsonisms were excluded. The parkinsonism was attributed to complications from lamivudine. Lamivudine associated parkinsonism has not been reported previously in the medical literature.

INTRODUCTION

Lamivudine is an effective and well-tolerated agent for treating chronic hepatitis B and acquired immunodeficiency syndrome. There are side effects in long-term use of lamivudine, including granulocytopenia, depression and peripheral neuropathy, lactic acidosis and pancreatitis.[1] Lamivudine induced parkinsonism has not been previously reported. This is a report of 3 cases of parkinsonism associated with long term usage of lamivudine seen in our department since 2000.

CASE REPORT 1

This 39-year-old male, was admitted because of progressive dizziness and lethargy for one month. He had been undergoing treatment of chronic hepatitis B with lamivudine 100 mg/day for half a year prior to onset of the presenting symptoms. Physical examination showed that he had a mask like face, shuffling gait, and hypokinesia with reduced automatic movements. There was increased muscle tone. The tendon reflexes were normal, and plantar responses were flexor. Examination of sensory and autonomic nervous system and coordination were also normal. Investigations including full blood count, liver enzymes, renal function test, fasting glucose, serum electrolytes, serum immunoglobulins were normal. The serum bilirubin was raised at 38.1 umol/l, direct bilirubin was 19.8 umol/l. The serum HBsAg, HBeAg and HBcAb were positive. Cerebrospinal fluid examination was also normal. The abdominal ultrasound examination showed generalized augmentation of light spots in the liver, consistent with cirrhosis from chronic hepatitis B infection. The serum carcinoma markers and lipoprotein did not show any abnormality to indicate a diagnosis of liver cancer or fatty liver. Brain MRI showed presence of an asymptomatic lacunar infarction in the left internal capsule. Investigations for Wilson's disease showed normal serum ceruloplasmin, absent Kayser-Fleischer rings and negative family history.

The patient was treated with levodopa and benserazide 0.5g/day for 15 days without clinical improvement. After that, lamivudine was stopped. The patient reported improvement of initiation of movement after one week. Benzhexol 6mg/day was then given. Ten days later, tiredness improved and hypokinesia was ameliorated. Six months later during follow-up, the patient no longer had mask face, shuffling gait and lethargy. Benzhexol was taken off without recurrence of symptom. The last follow up was after another 23 months since the first follow up.

CASE REPORT 2

This 31 years old male complained of lethargy and slow movement for one and half months after taking lamivudine 100mg/day for one year for treatment of chronic hepatitis B. There was no family history of Wilson's disease. Physical examination showed shuffling gait, increased muscle tone and hypokinesia with reduced automatic movements. The tendon reflexes were normal, and plantar responses were flexor. Sensory, autonomic system and coordination examinations were normal. Investigations inclusive of full blood count, renal function test, fasting blood glucose, serum electrolytes and serum ceruloplasmin were

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normal. There was increased serum bilirubin (39.2umol/l) and direct bilirubin (21.7umol/l) with normal liver enzymes. Serum HBsAg, HBeAg and HBcAb were positive. Brain MRI and Abdominal ultrasound examination were normal.

The patient was treated with benzhexol 6mg/day for 2 weeks without clinical improvement. Lamivudine was then stopped. One week later, hypokinesia was ameliorated. The patient did not show any relapse in symptoms and signs of parkinsonism in the 18-months follow-up after the benzhexol treatment was taken off.

CASE REPORT 3

This 34 years old male complained of progressive lethargy and clumsiness of movement for 3 months after taking lamivudine 100mg/day for two years for the treatment of chronic hepatitis B. There was no family history of Wilson's disease. On examination, the patient had a mask like face, cogwheel rigidity, shuffling gait, increased muscle tone and reduced automatic movement. The tendon reflexes, plantar responses, sensory, autonomic system examinations and coordination were normal. Kayser-Fleischer rings were not seen. Investigations showed normal full blood count, renal function test, fasting blood glucose, liver enzymes and serum bilirubin, serum ceruloplasmin were normal. The serum HBsAg and HBeAb were positive. No abnormality was found in abdominal ultrasound and brain MRI.

Lamivudine was stopped and the patient was given benzhexol 6mg/day. One week later, the clumsiness of movement and reduced automatic movement completely recovered. Benzhexol was taken off one month later. During the 2-years follow up, the patient did not show any symptoms of shuffling gait, lethargy and abnormal muscle tone.

DISCUSSION

All the 3 patients in this report showed features of parkinsonism with mask like facies, hypokinesia with reduced automatic movement and shuffling gait. The symptoms were ameliorated with benzhexol. There was no pyramidal sign or cognitive abnormality. When benzhexol was subsequently withdrawn, during long duration of follow up, the patient did not have relapse of the symptoms and signs. The clinical course of illness was thus inconsistent with the diagnosis of Parkinson's disease.

Our patients were of middle age with no risk factor for early onset atherosclerosis. There was also no history or signs of the usual manifestations of cerebrovascular disease. Brain MRI showed a lacunar infarct in Case 1, and normal in the other 2 patients. Cerebrovascular disease is thus unlikely to be the cause of parkinsonism seen in our patients.

Wilson's disease is an autosomal recessive disorder caused by excessive copper accumulation in the liver and brain and other organs. The responsible gene is ATP7B that is located in chromosome 13.[2] The diagnosis of Wilson's disease is unlikely in our patients as there was no family history of Wilson's disease, there was no pyramidal and cognitive abnormality, examination for Kayser-Fleischer rings were negative, the serum ceruloplasmin was normal, the parkinsonism reversed without copper chelating treatment, and there was no relapse of symptoms during long duration of follow up.

Younger-onset Parkinson disease is another differential diagnosis. This is often a familial disease and most patients had mutations in the gene encoding Parkin. Generally, a good response to levodopa is seen but fluctuation and dyskinesia is much more common and occurs early.[3] All our 3 patients did not have a family history of Parkinson disease. The long follow up with no relapse of parkinsonism despite being off benzhexol is against the diagnosis of younger-onset Parkinson disease. Our patients were also not on neuroleptic or other drugs that are known to block dopamine function and cause parkinsonism, such as metoclopramide and lithium.

All our 3 patients had insidious onset of symptoms following the use of lamivudine for more than half a year. The patients improved with withdrawal of lamivudine and treatment with benzhexol. There was no further development of parkinsonism or other movement disorders during their long duration of follow-up, even after withdrawal of benzhexol. Further investigations also did not demonstrate any other secondary causes of parkinsonism. The authors thus believe that the parkinsonism in these patients were due to the long term use of lamivudine, which has not been previously reported in medical literatures.

Lamivudine is a nucleotide reverse transcriptase inhibitors (NRTI). NRTIs has been shown to inhibit cellular polymerases, most notably mitochondrial DNA polymerase gamma. The proposed mechanisms of NRTIs induced mitochondrial toxicity include defects in mitochondrial DNA replication.[4] Furthermore, the clinical manifestations of NRTI-induced mitochondrial toxicity resemble those of inherited mitochondrial

disease.[5] Oxidative stress and mitochondrial dysfunction have also been implicated in the pathogenesis of Parkinson's disease.[6] We postulate that lamivudine, passing through the blood-brain barrier, induces mitochondrial toxicity to the brain, especially to the vulnerable cholinergic neurons in substantia nigra-corpus striatum pathway, resulting in parkinsonism.[7-9] An early recognition of such a potential adverse effect of lamivudine could reverse the otherwise progressive course.

In summary, this is a report of 3 patients who developed parkinsonism following use of lamivudine. All the 3 patients were taking lamivudine for treatment of chronic hepatitis B infection. The patients manifested parkinsonism after taking lamivudine for at least half a year. Withdrawal of lamivudine and benzhexol treatment led to clinical improvement. There was no recurrence of parkinsonism during the 18-24 months follow-up even when benzhexol was withdrawn. Wilson's disease and other secondary causes of parkinsonism were excluded.

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