

**페니토인 장기과다 복용 후 발생한 소뇌 위축 — 증례 보고 —**

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**Cerebellar Atrophy Following Long Term Phenytoin Overdose — A case report —**

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Phenytoin is a commonly used antiepileptic drug, and its narrow therapeutic index causes various toxicities. Although acute toxicity commonly causes ataxia, few cases have been reported of permanent cerebellar atrophy. A 49-year-old female with epilepsy was prescribed oral phenytoin. After three years of medication, seizure was controlled, but she developed unsteady gait and dysarthria. On admission, the patient showed severe bilateral ataxia, gingival hypertrophy, nystagmus, and dysarthria. Phenytoin toxicity was the impression, and phenytoin was omitted. Serum phenytoin level was 46.9 mg/L (therapeutic range being 10~20 mg/L). Brain magnetic resonance imaging (MRI) was performed to rule out other brain lesions, and diffuse cerebellar atrophy was revealed. After rehabilitation, mild bilateral ataxia remained, standing balance was poor, and the patient was able to walk 70 meters with minimal assist using roller walker. We review a case of chronic phenytoin toxicity that manifested as cerebellar ataxia and later showed atrophy of cerebellum. (**Brain & NeuroRehabilitation 2011; 4: 69-71**)

**Key Words:** cerebellar ataxia, epilepsy, phenytoin**Introduction**

Phenytoin is an antiepileptic drug with a narrow therapeutic index, and it can cause acute and chronic toxicities. Acute toxicities can be caused by high intravenous (IV) infusion rates or oral overdose. Hypotension, cardiac arrhythmias, central nervous system depression are known side effects of high IV infusion rates. Cerebellar, vestibular symptoms and signs such as nystagmus, ataxia, vertigo, and diplopia can be seen in cases of oral overdose. Chronic toxicities include dose related vestibular/cerebellar effects, behavioral changes, gingival hyperplasia, gastrointestinal disturbances, and sexual-endocrine effects such as osteomalacia, hirsutism, and hyperglycemia. Chronic high levels of phenytoin are also reported to cause cerebellar volume reduction.

Due to the possible side effects and diversity in metabolism of phenytoin, routine serum level monitoring is needed to maintain the therapeutic plasma concentration (10~20  $\mu$ g/ml).

There have been reports of cerebellar atrophy following both acute and chronic phenytoin overdose, and De Marcos et al.<sup>1</sup> reported correlation between cerebellar volume reduction and time of exposure to phenytoin.

We report a case of a patient that developed severe ataxia while on phenytoin medication, and was later diagnosed cerebellar atrophy secondary to phenytoin overdose. To our knowledge, there have been few reported cases similar to this patient in Korea.<sup>2</sup> The patient stopped taking phenytoin after the diagnosis, but symptoms remained after rehabilitation treatment.

**Case Report**

On March 13, 2009, a 49-year-old female was admitted to the hospital for gait disturbance and dysarthria that started a year ago. Three years ago she started generalized seizures and was prescribed oral phenytoin at another hospital with a dosage of 100 mg, three times daily.

접수일: 2010년 7월 5일, 1차 심사일: 2010년 8월 26일  
2차 심사일: 2010년 10월 4일, 게재승인일: 2010년 10월 11일  
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Seizures were provoked when medication was taken irregularly. From one year ago the patient kept on schedule and for the while remained seizure free. On March 25, 2008, following a head trauma with loss of consciousness from slipping down, she developed nausea and vomiting. Afterwards she developed generalized weakness, unsteady gait and dysarthria. Brain imaging studies at that time revealed no specific findings. From May, she had difficulty aiming the spoon to her mouth while eating, and her trunk kept swaying to the side in sitting position. On December, she received 18-Fluorodeoxyglucose positron emission tomography (PET) scan of the brain, which revealed decreased metabolism in the cerebellum (Fig. 1), and was referred to our hospital.

On admission, she was continuing phenytoin medication of same dose, and was also taking etizolam, clonazepam,

and bromocriptine. On physical examination, the patient showed severe bilateral ataxia, gingival hypertrophy (Fig. 2), nystagmus, dysarthria, and was unable to walk independently. Laboratory results showed serum phenytoin level of 46.9 mg/L, which was above the therapeutic level. Phenytoin toxicity was the impression, and phenytoin was omitted, substituted by oxcarbazepin.

On March 22, serum phenytoin decreased to the therapeutic range, and ataxia decreased in severity but persisted. Brain MRI was performed to rule out other brain lesions, and diffuse cerebellar atrophy was revealed (Fig. 3).

On March 31, the patient was transferred to the Rehabilitation department. After one month of rehabilitation therapy, mild bilateral ataxia remained, standing balance was poor, and the patient was able to walk 70 meters with minimal assist using a roller-walker. She needed minimal to moderate assist in daily activities. Her seizure was controlled with topiramate on discharge and

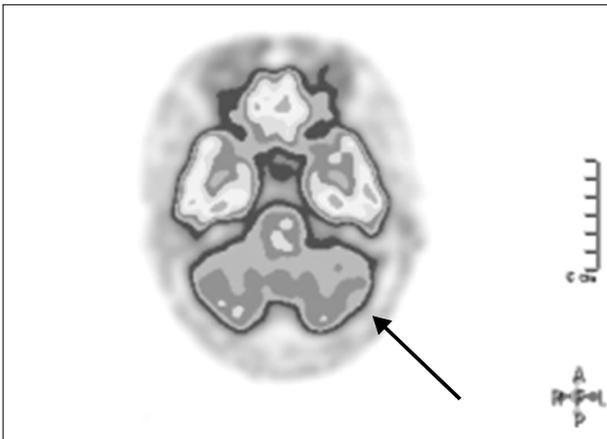


Fig. 1. PET scan showing decreased metabolism of cerebellum.



Fig. 2. Gingival hypertrophy of the patient.

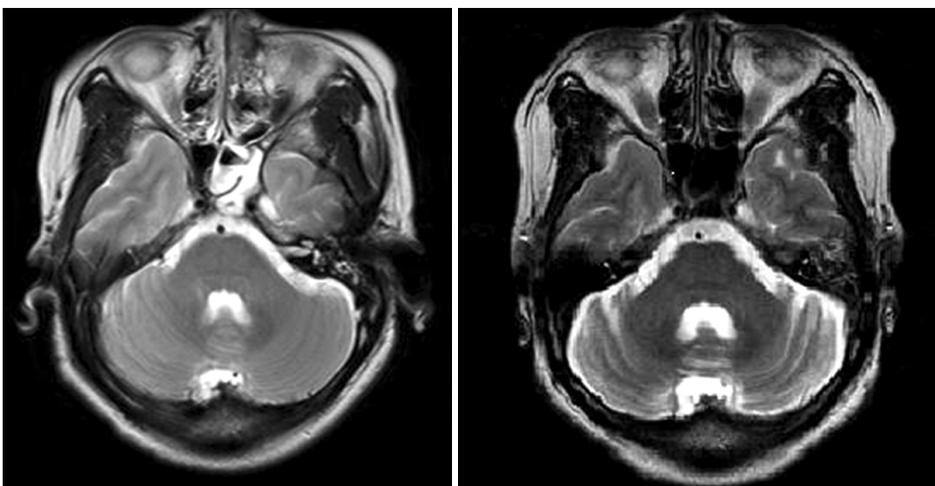


Fig. 3. Transverse T2-weighted MRI obtained on May 8, 2008 (left), and March 23, 2009 (right) reveals the development of diffuse cerebellar atrophy.

she required continuous rehabilitation.

## Discussion

Phenytoin is one of the first line antiepileptic drugs for many epileptic syndromes. Its high efficacy and low cost makes it widely used. As other antiepileptics, it has various side effects, especially when blood levels are too high.

Cerebellar atrophy may occur in phenytoin-exposed patients. Cerebellar degeneration after chronic phenytoin therapy was reported by McLain et al. in 1980.<sup>3</sup> Five patients all had high plasma levels of the drug, and none was having seizures at the time the cerebellar syndrome appeared. The authors acknowledged that hypoxia from repeated convulsions could cause cerebellar atrophy, but suggested that phenytoin therapy was also responsible for the degeneration. Botez et al. reported that posterior fossa atrophy in epileptics was significantly correlated with both the length of the illness and the amount of phenytoin ingested.<sup>4</sup> Masur et al. described a case of marked cerebellar atrophy after a single suicidal intoxication with phenytoin, and suggested that a severe acute intoxication with it may directly cause cerebellar degeneration.<sup>5</sup> Luef et al. found no correlation between degree of atrophy and severity of clinical symptoms and elevation of serum phenytoin levels.<sup>6</sup> Study of De Marcos et al. reported that decrease in cerebellar volume measured by MRI volumetry correlated with duration of treatment with phenytoin, and there was more severe atrophy in patients who had had phenytoin intoxication.<sup>1</sup>

It is unclear whether the use of phenytoin, the seizures, or the initial brain insult is the primary etiology.<sup>7-9</sup> In the study of mechanisms of cerebellar atrophy, the purkinje cells and granule cells are the main target of toxic agents. Purkinje cells are one of the largest neurons in the brain and are sensitive to ischemia, bilirubin, ethanol, and diphenylhydantoin.<sup>10</sup>

In our case the patient first developed cerebellar ataxia as a result of phenytoin toxicity from overdosing, although the duration of overdose is unclear. Brain images were

normal at that time but later studies showed cerebellar atrophy, without other brain lesions. The ataxia decreased but remained in severity after discontinuing the medication, affecting the patients gait and daily activities. The patient was seizure free at the time the symptoms developed, and the symptoms decreased in severity once phenytoin was stopped. These suggested that phenytoin was responsible for the degeneration, although the seizures might have had a role.

Our case shows how chronically high levels of phenytoin can manifest as cerebellar ataxia and later cause cerebellar degeneration. We can learn the importance of maintaining therapeutic levels by blood monitoring, to decrease the possibility of developing permanent cerebellar dysfunction.

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