

# Baclofen-induced Reversible Akinetic Mutism

Shih-Cheng Chen, Yao-Don Hsu, and Giia-Sheun Peng

**Abstract-** A 73-year-old woman who had type 2 diabetes with chronic renal insufficiency developed akinetic mutism after baclofen use for chronic lumbago. Her mental state recovered dramatically in two days after discontinuing baclofen. The electroencephalography (EEG) showed a background of diffuse slow waves with periodic triphasic waves. The brain magnetic-resonance imaging showed brain atrophy without features of acute strokes. Current diagnosis of baclofen-induced akinetic mutism is based on clinical history and the findings of EEG. The underlying pathophysiology is not yet clear, which may be caused by selective binding of the  $\gamma$ -aminobutyric acid-B receptors with interruption of thalamocortical limbic pathways in the frontal lobes. This report indicates that akinetic mutism might be induced by baclofen use in patients with severely impaired renal function.

**Key Words:** Akinetic mutism, Baclofen, Chronic renal insufficiency, Periodic triphasic waves

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## INTRODUCTION

Akinetic mutism is an unusual mental state in which the patient is mute, generally unresponsive and unwilling to perform even simple motor activity. However, alertness, visual fixation, motor and sensory functions and some fundamental cognitive abilities are preserved<sup>(1,2)</sup>. In previous reports, akinetic mutism was mostly caused by pathological lesions involving bilateral frontal or mesodiencephalic areas<sup>(3-8)</sup>. Here we demonstrate a patient who developed akinetic mutism without any pathological brain lesion after chronic use of baclofen, a  $\gamma$ -aminobutyric acid-B agonist acting as anti-spastic agent.

## CASE REPORT

A 73-year-old woman was sent to our emergency room (ER) on March 10, 2002 due to bizarre speech fol-

lowed by mental changes. The patient had histories of hypertension, coronary artery disease and type 2 diabetes under medical control. She had suffered from osteoporosis with a compression fracture over the lumbar spine and had received a spinal operation last year. The lower back pain bothered her a lot even after the operation, and she continuously took medication from the original hospital. Besides she also suffered from insomnia and took sleep pills for a long time. Several episodes of bizarre speech and behavior, including sparse speech, being expressionless and motiveless, had been observed before, which would last for 1-2 days and resolved naturally. She did not pay much attention to it and had not sought medical advice for it before. In the afternoon of March 10, she began to display sparse and irrelevant speech. The patient was later found mute at her house sitting at a chair without response except opening eyes to call. Urinary incontinence was observed

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From the Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, Taipei.

Reprint requests and correspondence to: Giia-Sheun Peng, MD, Department of Neurology, Tri-Service General Hospital, No. 325, Sec. 2, Cheng-Kung Road, Taipei, Taiwan.

E-mail: penggs@seed.net.tw

then. She was thus sent to our ER and admitted due to acute conscious changes.

On admission, vital signs were generally stationary without fever, and respiration was smooth. She was found inert lying on the bed, with both eyes closed but opened when she was called. Stereotype of spontaneous movement by scratching her leg with her right hand was observed. There was no verbal output except moaning due to deep pain stimulation. She looked at us with an apathetic expression, and the eyeballs reacted to auditory stimuli without limitation of eyeball movements in the horizontal plane. There were normal pupil sizes and light reflexes, and no nystagmus was found. She could not obey the orders after repeated commands with speech or gesture. Muscle strength was relatively preserved with withdrawal to painful stimuli, and paratonia was found during the passive range of motion. Deep tendon reflexes were generally hypoactive. Babinski and Hoffmann signs were absent, and primitive reflexes were not detected. There were neither meningeal signs nor neck stiffness.

Initial laboratory studies showed mild leukocytosis with a neutrophil predominance (white blood cell counts: 11600/ul, neutrophil: 84%, and lymphocyte: 9.9%. In addition, the electrolytes and liver function tests were

normal. However, the results of blood urea nitrogen (BUN) and creatinine (Cr) were abnormal (BUN: 44mg/dL, Cr: 3.3 mg/dL). The urinary analysis showed proteinuria but otherwise was clear. Electrocardiography showed a rhythm of atrial fibrillation. Brain computed tomography scanning performed at ER was unremarkable for her age.

The management for stroke was applied firstly including parenteral hydration, aspirin and intravenous pentoxifylline use. The drugs used before admission were all discontinued. The multi-modality brain magnetic resonance (MR) imaging for strokes were performed on March 11 and only senile cortical atrophy and a cerebral small vessel ischemic disease were disclosed. There was no evidence of acute ischemic strokes in the studies of diffusion-weighted MR and fluid-attenuated inversion recovery (FLAIR) imaging. The intracranial vessels were patent in the brain MR angiography. The carotid ultrasonography showed no atherosclerotic plaque in neck vessels. The electroencephalography (EEG) showed a mild slow background activity with sinusoidal 7-8 Hz waves and intermittent repetitive synchronous 2-Hz triphasic waves predominantly in the frontal regions (Fig. 1). Neither convulsion nor myoclonus was observed



**Figure.** This patient with chronic renal insufficiency presented with akinetic mutism after using baclofen. The EEG demonstrated transient repetitive polymorphic synchronous triphasic waves bilaterally that have their maximal amplitude in the frontal areas (channels 1, 5, 9 and 13). They repeated every 0.5 seconds, lasting 5-6 seconds. The background activities then showed regular sinusoidal 7-8 Hz over the bilateral occipital regions.

throughout the period of recording.

A dramatic mental recovery appeared on the third day of admission, and she began to speak and follow order appropriately. Therefore a lumbar puncture for cerebrospinal fluid study was held. She could not memorize the previous events during the attack. The 24-hour creatinine clearance was measured to be 16.86 ml/min with severe proteinuria (daily protein loss = 2.24 gm). Her recent oral medication included acetaminophen 1500 mg carbamazepine 300 mg and baclofen 15 mg in 3 divided dose daily, glipizide 5 mg once per day, meloxicam 7.5 mg twice daily and diazepam 5 mg, zolpidime hemitartrate 10 mg hs respectively. These medications had lasted at least for several months and before the spinal operation.

The Mini-Mental State examination on March 13 showed a mild mental impairment. Her mental state substantially improved. She complained of insomnia and lower back pain as usual, otherwise no abnormality was found compared with the premorbid condition. She was discharged smoothly on March 18.

## DISCUSSION

Cairns et al<sup>(9)</sup> firstly described the symptomatology of akinetic mutism in 1941 in a patient with a cyst in the third ventricle with complete immobility, inability to speak, yet showing adequate reactions to external stimuli. The akinetic state of the patient could immediately be remedied by a puncture of the cyst. The child could speak normally and did not show any other neurological deficits<sup>(2,9)</sup>.

Some important features of akinetic mutism were extracted from the descriptions of Cairns et al including: 1. appearance of alertness; 2. visual fixation to the examining person; 3. movements of the eyes in response to auditory stimuli; 4. movements after often repeated commands; 5. presentation of some degree of speech or speech effort<sup>(2)</sup>.

Pathologically, akinetic mutism was subdivided into frontal form and mesencephalic form by Segarra<sup>(3)</sup>. The vertical eyeball movement tends to be limited in the mesencephalic form, while profound apathy and lacking of most psychic drives or impulse to action are found in the frontal form<sup>(2,8)</sup>. The etiologies of the frontal form included infarctions in the bilateral anterior cerebral arteries, and a glioblastoma with bilateral frontal lobe infiltration.

Examples of mesodiencephalic lesions were found in the cases of third ventricle tumor, damage to the thalamus and hypothalamus, lesions in the late stage of an obstructive hydrocephalus, and circulatory disturbances in the mesodiencephalic region<sup>(3-7)</sup>.

Our patient displayed a state of immobility, profound apathy and lacking of speech effort indicating a frontal form of akinetic mutism. Other mental states may also present similar features of alertness with immobility and no speech output, such as locked-in syndrome, persistent vegetative state, and catatonia<sup>(8)</sup>. Comparatively, akinetic mutism is characterized by a better preservation of visual fixation, basic motor and sensory functions, and perhaps some fundamental cognitive abilities, but lack of motivation<sup>(1,2)</sup>.

Baclofen, a  $\gamma$ -aminobutyric acid (GABA) derivative, is commonly used in treating muscular spasticity. The mechanism of action is thought to be activation of GABA-B receptors leading to a reduction in neurotransmitter release, such as glutamate and substance P, through presynaptic hyperpolarization<sup>(1)</sup>. This inhibitory action of baclofen mainly works at spinal sites. However, owing to the penetration through blood-brain-barrier, some central nervous system (CNS) effects do happen. The most common symptoms were daytime sedation, drowsiness, and respiratory depression. Patients with acute baclofen intoxication may present with impaired consciousness, respiratory depression, hypotonia and hyporeflexia<sup>(10)</sup>. Normally within 72 hours, 70 to 80% of the ingested baclofen is excreted in the urine mainly in an unchanged form while 15% is metabolised in the liver. In patients with severely impaired renal function, toxic symptoms have been observed soon after baclofen use, even with a low initiation dosage<sup>(11)</sup>.

To our knowledge, there have been only two cases of baclofen-induced akinetic mutism. The first was a 76-year-old man with normal renal function who was chronic bed-ridden. Akinetic mutism appeared progressively after 3 days of baclofen use for treating spasticity. This condition resolved gradually 4 days after discontinuing baclofen use<sup>(1)</sup>. The second was a 57-year-old woman with an end stage renal disease who developed akinetic mutism after taking a single dose of baclofen (10mg) for muscle spasms. The condition resolved substantially after repeated dialysis<sup>(12)</sup>.

A typical EEG is helpful in the diagnosis of the baclofen effect<sup>(13)</sup>. In patients with baclofen intoxication

or encephalopathy, distinct EEG findings, such as generalized bursts of sharp discharges and periodic triphasic waves were reported<sup>(1,11,14)</sup>. The periodic sharp waves were relatively specific findings in EEG, which occurred in a few entities, including toxicity of lithium and ifosfamide; metabolic encephalopathy due to hepatic failure, uremia, or hypoxia. Besides, periodic triphasic waves of about 1 Hz in EEG are also known to be presented in Creutzfeldt-Jakob disease, in which akinetic mutism has been postulated to be one criteria in the diagnosis of this disease<sup>(2)</sup>.

In our patient, the previous episodes of motivelessness were thought to be from the similar but milder CNS effect of baclofen. The deterioration in renal function or overdose of baclofen was suspected to cause akinetic mutism. The multiple drug use should be also taken into consideration, but the EEG findings of periodic triphasic waves have not been displayed in intoxication of benzodiazepine or carbamazepine in our knowledge. CNS depressants have been reported to interact with baclofen and accelerate its toxicity in patients with severely impaired renal function<sup>(11)</sup>. According to the previous reports and our experience, the reversible akinetic mutism without explicatory brain lesion, a typical EEG findings and a compatible drug history could assure the diagnosis of baclofen intoxication. The neurotoxicity of baclofen was reported to have an excellent prognosis in case of early recognition and discontinuation of it<sup>(14)</sup>.

The exact mechanism of baclofen-induced akinetic mutism is not fully understood yet, but reducing excitability of cortical interneurons or thalamocortical projections may lead to mutism. Akinetic mutism has been attributed to bilateral lesions in ventromedial frontal regions or fronto-diencephalic connections<sup>(8)</sup>. Why baclofen selectively affects this mesolimbic pathway is still unknown<sup>(1)</sup>. Besides, the complication was rare and idiosyncratic. An elderly patient with cognitive disorders might be more vulnerable to the adverse effect<sup>(1)</sup>. The effect may imply specific pathway of neurotransmission regulating motivation and cognition.

In conclusion, akinetic mutism is a pathognomonic mental state that indicates distinct neurophysiological deficits. Baclofen is a widely used muscle relaxant with relative safety, but for those with severely impaired renal function, it should be avoided, whereas alternative therapy is suggested<sup>(11)</sup>.

## REFERENCES

1. Rubin DI, So EL. Reversible akinetic mutism possibly induced by baclofen. *Pharmacotherapy* 1999;19:468-70.
2. Otto A, Zerr I, Lantsch M, et al. Akinetic mutism as a classification criterion for the diagnosis of Creutzfeldt-Jakob disease. *J Neurol Neurosurg Psychiatry* 1998;64:524-8.
3. Segarra JM. Cerebral vascular disease and behavior. 1. The syndrome of the mesencephalic artery (basilar artery bifurcation). *Arch Neurol* 1970;22:408-18.
4. Borggreve F, De Deyn PP, Marien P, et al. Bilateral infarction in the anterior cerebral artery vascular territory due to an unusual anomaly of the circle of Willis. *Stroke* 1994;25:1279-98.
5. Lechi A, Pilleri G, Carreras M. Akinetic mutism due to glioma of the midline. *Archiv fur Psychiatrie und Nervenkrankheiten* 1975;220:1-7.
6. Shinoda M, Tsugu A, Oda S, et al. Development of akinetic mutism and hyperphagia after left thalamic and right hypothalamic lesions. *Childs Nerv Syst* 1993;9:243-5.
7. Anderson B. Relief of akinetic mutism from obstructive hydrocephalus using bromocriptine and ephedrine. Case report. *J Neurosurg* 1992;76:152-5.
8. Victor M, Ropper AH. Neurologic disorders caused by lesions in particular parts of the cerebrum. In: Adams RD, Victor M, eds. *Principles of Neurology*. 7th ed. New York: McGraw-Hill, 2001:464-98.
9. Cairns H, Oldfield RC, Pennybacker JB, et al. Akinetic mutism with an epidermoid cyst of the 3rd ventricle: with a report on the associated disturbance of brain potentials. *Brain* 1941;64:273-90.
10. Lee TH, Chen SS, Su SC, et al. Baclofen intoxication: report of four cases and review of the literature. *Clin Neuropharmacol* 1992;15:56-62.
11. Chen KS, Bullard MJ, Chien YY, et al. Baclofen toxicity in patients with severely impaired renal function. *Ann Pharmacother* 1997;31:1315-20.
12. Parmar MS. Akinetic mutism after baclofen. *Ann Intern Med* 1991;115:499-500.
13. Zak R, Solomon G, Petito F, et al. Baclofen induced generalized nonconvulsive status epilepticus. *Ann Neurol* 1994;36:113-4.
14. Hormes JT, Benarroch EE, Rodriguez M, et al. Periodic sharp waves in baclofen-induced encephalopathy. *Arch Neurol* 1988;45:814-5.