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AKINETIC MUTISM DUE TO DIPHENYLHYDANTOIN TOXICITY*

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SUMMARY: Tütüncüoğlu S, Kantar M, Tekgül H, Candan C. (Neurology Unit, Department of Pediatrics, Ege University Faculty of Medicine, İzmir, Turkey). Akinetic mutism due to diphenylhydantoin toxicity. Turk J Pediatr 1997; 39: 403-407.

Akinetic mutism (AM) is a rare, specific, unconscious state. An AM patient seems to be awake, lacks mental activity, is unable to speak, and does not respond to any environmental stimulus. Cyclical sleep and awake states are maintained, and incontinence is present. Various factors such as tumor, vascular events, drug use and radiotherapy are responsible for the development of AM.
A 12-year-old epileptic patient displayed AM and diphenylhydantoin toxicity (DPH). She seemed awake, was unable to speak or to understand, and had no movements with either spontaneous or noxious stimuli. Her serum DPH level was greater than 40 µg/ml. Magnetic resonance imaging (MRI) showed mild cerebellar atrophy. All known causes of AM were excluded. The AM state in this patient was considered to be due to toxic DPH levels. She regained her motor and mental activity within two months after carbamazepine was administered to replace DPH. She was symptom-free when examined at the two-year follow-up. No similar adverse effect of DPH has been reported to date. *Key words: diphenylhydantoin, akinetic mutism, adverse effect.*

Akinetic mutism (AM) is a rare, specific, unconscious state. An AM patient appears to be awake, lacks mental activity, is unable to speak, and does not respond to any environmental stimulus. Cyclical sleep and awake states are maintained, and incontinence is present. Possible causes of AM include cerebrovascular accident, craniopharyngioma, cardiac arrest, severe hypoglycemia, carbon monoxide intoxication, several drugs, central pontine myelinolysis (CPM), radiotherapy, trauma, tumor, hydrocephaly, Wernicke-Korsakoff disease and tuberculous endocarditis[1-7]. A case with AM possibly due to diphenylhydantoin (DPH) toxicity is presented.

Case Report

A 12-year-old female had been taking DPH at a dose of 300 mg/d for generalized convulsions. She had recently been admitted to a state hospital for gait disorder

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and ataxia, having deteriorated over the previous three months. She had dysarthria, truncal ataxia and horizontal nystagmus on examination. DPH was discontinued as the serum level was greater than 40 µg/ml. The patient experienced fever on day 10 of admission, which was considered to be due possibly to a lung infection. Later she was admitted to our hospital. On admission she appeared to be awake, but was unable to speak or to understand any speech and uncooperative. No extremity movements were observed with either spontaneous or noxious stimuli. She had orofacial dyskinesia and incontinence, and displayed cyclical sleep/awake states. Other physical findings were normal.

Laboratory examinations including routine blood and urine analysis, liver enzymes, ammonia, urea, lipid fractions, LDH, immunoglobulins, thyroid hormone levels, lactic acid, serum B_{12} level, and serum and urine aminoacid chromatographies were normal. Group agglutination tests, monospot test, HBsAg, anti-HCV, anti HIV I-II antibodies, VDRL test, anti-CMV antibodies, and anti-HSV antibody in cerebrospinal fluid (CSF) were negative. The CSF-IgG index and CSF-myelin basic protein (MBP) were normal. The ECG, EEG (on day 1,5, and 25), EMG, VEP, SEP recordings and Tc^{99m} HMPAO-Brain SPECT were normal. Cranial MRI (on days 1,7 and 21) showed only cerebellar atrophy (Figs. 1, 2). Brainstem auditory evoked potential (BAEP) recording showed prolonged bulbopontine transmission and normal wave 1 latency. The serum folic acid level was 1.1 ng/ml (normal: 2.5 ng/ml). Megaloblastic changes were not observed. No clinical or laboratory data compatible with lung infection were present. After

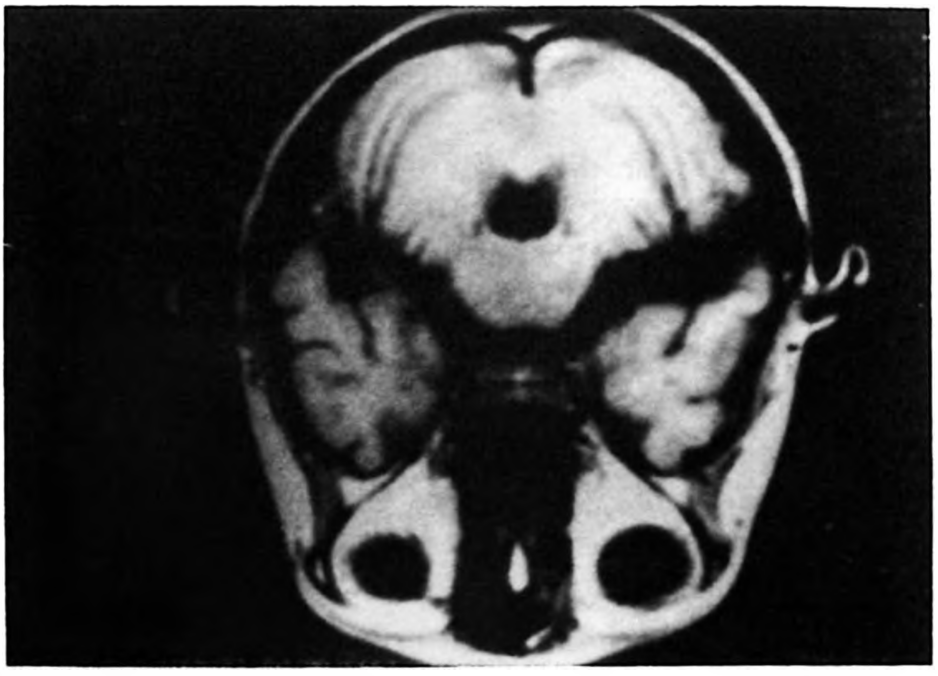

Fig. 1: Cerebellar foliae are prominent (Cranial MR-T1W1).

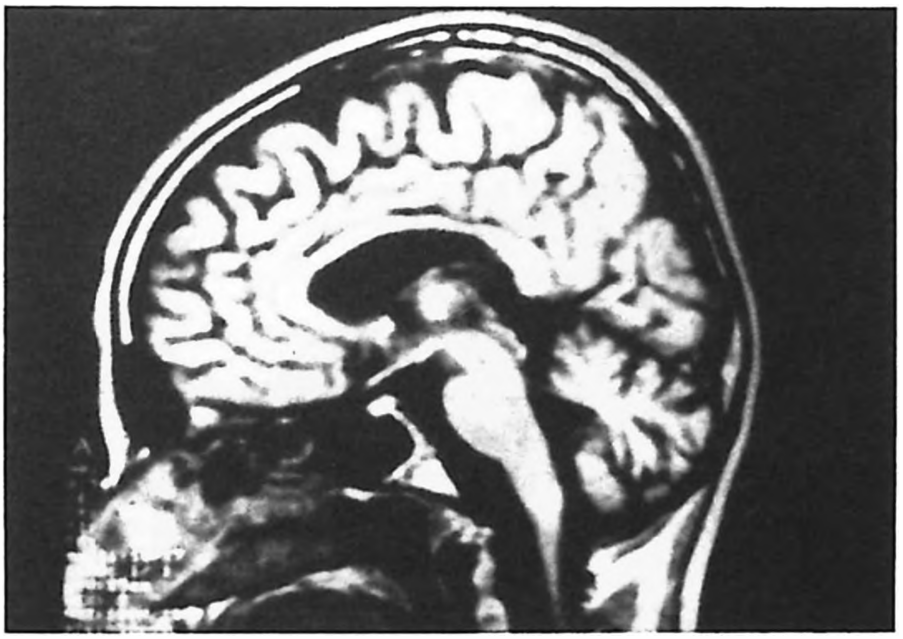

Fig. 2: Note mild cerebellar atrophy (Cranial MR-T1W1).

cessation of DPH, its serum level declined quickly. Carbamazepine administration at a dose of 300 mg/dl, and folic acid at 5 mg/d were instituted. Her spontaneous limb movements began on day 5, and orofacial dyskinesia was resolved within one week. She was able to walk and obey commands within the second month and to pronounce single words in the 10th week after admission. At the end of the 2nd month she had no cerebellar dysfunction. Four months later she was able to speak and had no seizures. Her repeated BAEP response was found to be normal.

Discussion

Diphenylhydantoin is a well-known anticonvulsant drug which has several adverse effects. These effects include nausea, vomiting, nystagmus, diplopia, ataxia, drowsiness, encephalopathy (depressed mental function, increase in seizures), depression, confusion, dyskinesia, myoclonus, dystonia, total external ophthalmoplegia, myasthenic state, and progressive or transient hemiparesis[8]. Akinetic mutism is characterized by a lack of responsiveness in the presence of preserved vigilance caused by many factors[2-7]. AM due to DPH use has not been reported to date.

Our patient displayed the AM state. All known vascular, cardiac, toxic, traumatic, infectious, tumoral and demyelinating factors that may cause AM were excluded. Our patient had only mild cerebellar atrophy and a low serum folic acid level,

which were attributable to long-term DPH use. Central pontine myelinolysis (CPM) may also cause AM[3]. Our patient had a normal CSF-IgG index, MBP levels and cranial MRIs. She only showed an abnormal BAEP response, which itself was not sufficient to make the diagnosis of CPM without other supportive tests. She had been taking DPH for 11 years, and her serum DPH level was greater than 40 µg/ml. She had cerebellar findings and orofacial dyskinesia, which are compatible with toxic DPH levels.

No association between DPH and AM has been defined in recent years. Folic acid depletion in the presence or absence of anemia has also not been reported to be related with AM. The anticonvulsant action of DPH pertains to the movement of sodium and calcium across cellular membranes by either passive or active transport. The pathophysiological mechanisms responsible for the AM state are not well understood. However, reduced arousal of cortical functions due to lesions at or rostral to the mesodiencephalic junction or impaired activation of the motor system following bilateral damage to the frontal lobes have been considered in the pathogenesis[9]. SPECT analysis has been found to demonstrate decreased blood supply to the frontal lobes[10]. Although the exact pathophysiological implications are not yet known, clinical trials with bromocriptine, a dopamine receptor agonist, have been promising and indicate the involvement of dopaminergic pathways[11]. Our patient had a normal SPECT analysis, demonstrating the absence of an organic, frontal lobe lesion. She also recovered spontaneously without taking bromocriptine.

We were unable to detect any known cause of AM in our patient. She displayed some signs of toxic DPH levels. We concluded that DPH may have been responsible for AM in our patient.

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