

1 CASE REPORT

2 Dopa-Responsive Dystonia subsequent to 3 Lamotrigine Administration: Case Reports

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6 Received October 22, 2012; Accepted November 10, 2012

7 This paper is available online at <http://ijpt.tums.ac.ir>

8 ABSTRACT

9 Epilepsy is a common neurologic disorder affecting approximately 1% of the population. The prevalence
 10 of active epilepsy in Kerman, Iran is 7.87/1000 individuals. The past decade has brought many advances
 11 to the treatment of epilepsy, including many new pharmacological agents. Lamotrigine is one of the new
 12 antiepileptic drugs. Lamotrigine has many side effects; the most important of which are allergic reactions.
 13 In this article, the author reports two cases of dopa- responsive dystonia (DRD) after few months
 14 administration of lamotrigine for epilepsy. The cases are two girls (4 and 5 years old) who had seizures
 15 and received lamotrigine 50 mg/day. They have been free of seizure after treatment but after some time
 16 the dystonic attacks developed. Lamotrigine administration discontinued, but dystonic attacks didn't
 17 disappear. Levodopa /carbidopa was started. After a few days, the dystonic pastures disappeared. In
 18 conclusion, lamotrigine may introduce dystonia in susceptible patients. These dystonic attacks might
 19 be responsive to levodopa.

20 **Keywords:** ?????

21 Epilepsy is a common neurologic disorder affecting 42 other medications such as valproic acid. It's
 22 about 1% of the population [1]. The prevalence of 43 predominantly metabolized in the liver by
 23 active epilepsy in Kerman, Iran is 7.87/1000 individuals 44 glucuronidation [9]. Lamotrigine has many side effects,
 24 [2]. Pharmacotherapy with antiepileptic drugs remains 45 most importantly allergic reactions. Gradual introducing
 25 the major treatment modality for epilepsy. This could 46 lamotrigine is one of the keys to reduce the frequency
 26 occur as a result of decreased excitation concurrent with 47 and severity of allergic reactions [5]. Although the
 27 increased inhibition [3]. Management of epilepsy differs 48 overall incidence of cutaneous reactions to lamotrigine
 28 from the treatment of other chronic diseases in that a 49 is high, the incidence of serious eruptions such as
 29 single breakthrough event has a major negative effect 50 erythema multiform, Stevens-Johnson syndrome, and
 30 on quality of life. Complete control of seizures is 51 toxic epidermal necrolysis is low [10,11]. The revision
 31 necessary as a single seizure impacts negatively on 52 of La Roche and Helmers demonstrated that side-effects
 32 patient quality of life and independence [4]. 53 led to drug withdrawal in 10.2% of all patients under

33 The past decade has brought many advances to the 54 lamotrigine therapy. Rash was the main reason for
 34 treatment of epilepsy, including many new 55 treatment discontinuation. It has been postulated that
 35 pharmacological agents. Lamotrigine is one of the new 56 side-effects may be lessened by slow introduction and
 36 antiepileptic drugs; it's been used more than two 57 titration [12,13].

37 decades [5-7]. Lamotrigine is a broad-spectrum 58 The present study reports two cases of dopa-
 38 antiepileptic drug of the phenyltriazine class chemically 59 responsive dystonia (DRD) after lamotrigine
 39 unrelated to other anticonvulsants [8]. Lamotrigine has 60 administration for a few months due to epilepsy. DRD
 40 an average elimination half-life of 33 hours, although 61 is a broad term used to described forms of dystonia
 41 this can be influenced by concomitant therapy with 62 characterized by the onset dystonia in early childhood

with dramatic and sustained response to treatment with levodopa. This disorder was first described by Segawa [14]. The most common form of DRD is an autosomal dominant condition (DYST5) caused by mutation of the gene for guanosine triphosphate cyclohydrolase [15].

CASE REPORTS

Case 1

A 5 years old girl who used lamotrigine 50 mg per day due to tonic-clonic seizure and had her first attack of seizure two months before her first visit. After starting lamotrigine, the patient was free from seizure for one year. Dystonic posture was developed in lower limb and after a time spread to lumbar spine, and then to the cervical area. Dystonic attacks worsened later in the day. Results of physical examinations, brain's MRI scans and hematologic and serologic laboratory tests were normal. Dystonic posture did not disappear after lamotrigine was discontinued. The dystonic attacks disappear after two days, when 50 mg per day levodopa/carbidopa was started.

Case 2

A 4 years old girl used lamotrigine 50 mg per day due to complex partial seizure. She had had her first attack of seizure a few months before her first visit. After receiving lamotrigine for two months, dystonic posture developed in lower limb and then spread to lumbar spine. Dystonic posture worsened later in the day. Physical examinations, brain's MRI scans, hematologic and serologic laboratory tests were normal. Dystonic posture did not disappear after lamotrigine discontinued. The dystonic attacks disappear after three days, when 50 mg per day levodopa/carbidopa was started.

DISCUSSION

DRDs are a group of disorders that show a good response to levodopa. The causes of these disorders are unknown, but the mutation of a gene is recognized in some studies. Onset of this disease usually happens in the first decade of life starting with foot dystonia, which progress to involve other body parts, but typically remains more severe in the lower extremities. The severity increases progressively over the first two decades of life, but plateaus with relatively few side effects and no long-term complication [16]. Untreated individuals developed diurnal fluctuations with marked improvement in the morning and worsening in the evening. DRDs are more frequent in female than in males, with a ratio varying from 1 to 4.3:1. Diagnosis of DRD can often be made on clinical grounds [17]. There are reports about DRD induction by diazepam [18], bupropion [19], cetirizine [20], riluzole [21], and tetrabenazine [22]. The authors, however, didn't find any reports about post-lamotrigine conditions. Lamotrigine is a new antiepileptic agent that is

frequently used in epileptic patients with a good tolerability and efficacy. Lamotrigine has side effects, the most important of which is exfoliative dermatitis and rashes [23]. A study showed dizziness in 11%, and ataxia in 12% of cases, but if treatment begins with low doses, these events decrease [24]. Other side effects were also reported such as sudden death due to cardiac dysrhythmia in two cases [25], psychosis as one of the rare side effects of lamotrigine [13], oral ulcers [26], chorea [27], leucopenia and thrombocytopenia [28], anticonvulsant hypersensitivity syndrome [29], abnormal eye movements and hyper-sexuality [30]. This dystonic effect may be due to the lack of selectivity of lamotrigine to block glutamate release in susceptible individuals. In dystonic mutant hamsters when subsided, dystonia can be re-invoked when these animals receive sodium channel blockers such as lamotrigine [31-34]. The patients under discussion are two girls (4 and 5 years old) who had seizure and received lamotrigine for a time and were free of seizure attacks. Dystonic attacks disappeared after receiving 50 mg/per levodopa/carbidopa. In conclusion, lamotrigine may introduce dystonia in susceptible patients. The dystonic attacks are responsive to levodopa.

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