

1 CASE REPORT

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

4 HOSSEIN ALI EBRAHIMI* and SAEED EBRAHIMI

5 *For author affiliations, see end of text.*

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 beresponsive 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

63 with dramatic and sustained response to treatment with
64 levodopa. This disorder was first described by Segawa
65 [14]. The most common form of DRD is an autosomal-
66 dominant condition (DYST5) caused by mutation of the
67 gene for guanosine triphosphate cyclohydrolase [15].

68 CASE REPORTS

69 Case 1

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

83 Case 2

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

96 DISCUSSION

97 DRDs are a group of disorders that show a good
98 response to levodopa. The causes of these disorders are
99 unknown, but the mutation of a gene is recognized in
100 some studies. Onset of this disease usually happens in
101 the first decade of life starting with foot dystonia, which
102 progress to involve other body parts, but typically
103 remains more severe in the lower extremities. The
104 severity increases progressively over the first two
105 decades of life, but plateaus with relatively few side
106 effects and no long-term complication [16]. Untreated
107 individuals developed diurnal fluctuations with marked
108 improvement in the morning and worsening in the
109 evening. DRDs are more frequent in female than in
110 males, with a ratio varying from 1 to 4.3:1. Diagnosis of
111 DRD can often be made on clinical grounds [17].
112 There are reports about DRD induction by diazepam
113 [18], bupropion [19], cetirizine [20], riluzole [21], and
114 tetrabenazine [22]. The authors, however, didn't find
115 any reports about post-lamotrigine conditions.
116 Lamotrigine is a new antiepileptic agent that is

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

141 REFERENCES

- 142 1. Ropper AH, Brown RH. Adams and Victor's Principles of
143 Neurology, 8th edition McGraw-Hill publisher 2005, page 271.
- 144 2. Ebrahimi HA, Shafa MA, Hakimzadeh-Asl S. Prevalence of
145 active epilepsy in Kerman, Iran: a house-based survey. *Acta*
146 *Neurol Taiwan* 2012; 21:115-24.
- 147 3. Greenhill SD, Jones RS. Diverse antiepileptic drugs increase the
148 ratio of background synaptic inhibition to excitation and
149 decrease neuronal excitability in neurones of the rat entorhinal
150 cortex in vitro. *Neuroscience* 2010; 167:456-74.
- 151 4. Gilliam F. Optimizing health outcomes in active epilepsy.
152 *Neurology* 2002; 58:S9-20.
- 153 5. Michoulas A, Farrell K Medical Management of Lennox-
154 Gastaut Syndrome. *CNS Drugs* 2010; 24:363-74.
- 155 6. Saetre E, Abdelnoor M, Perucca E, Taubøll E, Isojärvi J,
156 Gjerstad L. Antiepileptic drugs and quality of life in the elderly:
157 Results from a randomized double-blind trial of carbamazepine
158 and lamotrigine in patients with onset of epilepsy in old age.
159 *Epilepsy Behav* 2010; 17:395-401.
- 160 7. Marson AG, Al-Kharusi M, Alwaidh M, Appleton R, Baker
161 GA, Chadwick DW, Cramp C, Cockerell O, Cooper PN,
162 Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJL,
163 Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach
164 JP, Nicolaidis P, Roberts R, Shackley P, Shen J, Smith DF,
165 Smith PEM, Smith CT, Vanoli A, Williamson PR. The SANAD
166 study of effectiveness of carbamazepine, gabapentin,
167 lamotrigine, oxcarbazepine, or topiramate for treatment of
168 partial epilepsy: an unblinded randomised controlled trial.
169 *Lancet* 2007; 369: 1000-15.
- 170 8. Binnie CD. Lamotrigine. In: Engel J, Jr, Pedley TA, editors.
171 *Epilepsy: A comprehensive textbook*. Philadelphia: Lippincott-
172 Raven Publishers; 1997. p. 1531-40.
- 173 9. Werz MA. Pharmacotherapeutics of epilepsy: use of lamotrigine
174 and expectations for lamotrigine extended release. *Ther Clin*
175 *Risk Manag* 2008; 4:1035-46.
- 176 10. Schachter SC, Leppika IE, Matsuoa F, Messenheimer JA,
177 Faughta E, Moorea EL, Risner ME. Lamotrigine: A six-month,
178 placebo-controlled, safety and tolerance study. *J Epilepsy* 1995;
179 8:201-9.

- 180 11. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005; 64:1134-8.
- 184 12. LaRoche SM, Helmers SL. The new antiepileptic drugs: clinical applications. *JAMA* 2004; 291:615-20.
- 186 13. Brand G, Fueratsch N, Boechema V, Kramine C, Pieridou M, Vikkagran A, Woermann F, Pohlmann Eden B. psychosis is a rare events under lamotrigine treatment. *Epilepsy Behav* 2007; 11:930-476.
- 190 14. Mink JW. Dopa-responsive dystonia in children. Current treatment options in *Neurology* 2003; 5:279-82.
- 192 15. Ichinosa H, Ohye T, Tavarasshi E, Seki N, Hori T, Segawa M, Nomura Y, Endo K, Tanaka H, Tsuji S, et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase 1 gene. *Nat Genet* 1994; 8:230-42.
- 197 16. Segawa M. Hereditary progressive dystonia with marked diurnal fluctuations. *Brain Dev* 2002; 22:565-80.
- 199 17. Furukawa Y, Lang AE, Trugman JM. Gender-related penetrance and de novo GTP cyclohydrolase 1 gene mutations in dopa-responsive dystonia. *Neurology* 1998; 50:1015-20.
- 202 18. Hooker EA, Danzl DF. Acute dystonic reaction due to diazepam. *J Emerg Med* 1988; 6:491-3.
- 204 19. Detweiler MB, Harpold GJ. Bupropion-induced acute dystonia. *Ann Pharmacother* 2002; 36:251-4.
- 206 20. Esen I, Demirpence S, Yis U, Kurul S. Cetirizine-induced dystonic reaction in a 6-year-old boy. *Pediatr Emerg Care* 2008; 24:627-8.
- 209 21. Richter A, Gernert M, Löscher W. Prodystonic effects of riluzole in an animal model of idiopathic dystonia related to decreased total power in the red nucleus? *Eur J Pharmacol* 1997; 332:133-41.
- 213 22. Burke RE, Reches A, Traub MM, Ilson J, Swash M, Fahn S. Tetrabenazine induces acute dystonic reactions. *Ann Neurol* 1985; 17:200-2.
- 216 23. Varghas SP, Haith LR, Potten ML, Guiday RE, Ackerman BH. lamotrigine-induce toxic epidermolysis in three patients treated for bipolar disorder. *Pharmacotherapy* 2006; 26:609-704.
- 222 25. Zaccara G, Gangew PF, Cinoth M. Central nervous system adverse effects of new antiepileptic drugs. *Seizure* 2008; 17:405-21.
- 223 25. Aurlian D, Taubell E, Gyenstad L. Lamotrigine in idiopathic epilepsy increased risk cardiac death? *Acta Neurol Scand* 2007; 116:345.
- 225 26. O'Neill A, de Leon J. Two case reports of oral ulcer with lamotrigine several weeks after oxcarbazepine withdrawal. *Bipolar Disord* 2007; 9:310-3.
- 227 27. Cardoso F. Chorea, non genetic causes. *Cur Opin Neurol* 2004; 17:433-6.
- 230 28. Ural Au, Avcu F, Gekcil Z, Nerruz O. Leukopenia and thrombocytopenia possibly associated with lamotrigine use in a patient. *Epileptic Disord* 2005; 7:33-5.
- 233 29. Chang CC, Shiah IS, Yeh CB, Cross JH. Lamotrigine-associated anticonvulsant hypersensitivity syndrome in bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; 30:741-4.
- 236 30. Das B, Harris C, Smith DP, Cross JH. Unusual side effects of lamotrigine therapy. *J Child Neurol* 2003; 18:479-80.
- 238 31. Richter A, Löscher W. The novel antiepileptic drug, lamotrigine, exerts prodystonic effects in a mutant hamster model of generalized dystonia. *Eur J Pharmacol* 1994; 264:345-51.
- 243 32. Siep E, Richter A, Löscher W, Speckmann EJ, Köhling R. Sodium currents in striatal neurons from dystonic dt(sz) hamsters: altered response to lamotrigine. *Neurobiol Dis* 2002; 9:258-68.
- 246 33. Bhlumberger E, Chavez F, Palacios L, Rey E, Pajot N, Dulac O. Lamotrigine in treatment of 120 children with epilepsy. *Epilepsia* 1994; 35: 359-67.
- 249 34. Leach MJ, Baxter MG, Critchley MAE. Neurochemical and behavioral aspects of lamotrigine. *Epilepsia* 1991; 32: S4-8.

CURRENT AUTHOR ADDRESSES

Hossein Ali Ebrahimi, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran. E-mail:

Saeed Ebrahimi, Medical student of Tehran University of Medical Sciences, Tehran, Iran.