

## 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 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 117 frequently used in epileptic patients with a good  
64 levodopa. This disorder was first described by Segawa 118 tolerability and efficacy. Lamotrigine has side effects,  
65 [14]. The most common form of DRD is an autosomal- 119 the most important of which is exfoliative dermatitis  
66 dominant condition (DYST5) caused by mutation of the 120 and rashes [23]. A study showed dizziness in 11%, and  
67 gene for guanosine triphosphate cyclohydrolase [15]. 121 ataxia in 12% of cases, but if treatment begins with low

## 68 CASE REPORTS

### 69 Case 1

70 A 5 years old girl who used lamotrigine 50 mg per 122  
71 day due to tonic-clonic seizure and had her first attack 123  
72 of seizure two months before her first visit. After 124  
73 starting lamotrigine, the patient was free from seizure 125  
74 for one year. Dystonic posture was developed in lower 126  
75 limb and after a time spread to lumbar spine, and then to 127  
76 the cervical area. Dystonic attacks worsened later in the 128  
77 day. Results of physical examinations, brain's MRI 129  
78 scans and hematologic and serologic laboratory tests 130  
79 were normal. Dystonic posture did not disappear after 131  
80 lamotrigine was discontinued. The dystonic attacks 132  
81 disappear after two days, when 50 mg per day 133  
82 levodopa/carbidopa was started. 134

### 83 Case 2

84 A 4 years old girl used lamotrigine 50 mg per day 135  
85 due to complex partial seizure. She had had her first 136  
86 attack of seizure a few months before her first visit. 137  
87 After receiving lamotrigine for two months, dystonic 138  
88 posture developed in lower limb and then spread to 139  
89 lumbar spine. Dystonic posture worsened later in the 140  
90 day. Physical examinations, brain's MRI scans, 141  
91 hematologic and serologic laboratory tests were normal. 142  
92 Dystonic posture did not disappear after lamotrigine 143  
93 discontinued. The dystonic attacks disappear after three 144  
94 days, when 50 mg per day levodopa/carbidopa was 145  
95 started. 146

## 96 DISCUSSION

97 DRDs are a group of disorders that show a good 156  
98 response to levodopa. The causes of these disorders are 157  
99 unknown, but the mutation of a gene is recognized in 158  
100 some studies. Onset of this disease usually happens in 159  
101 the first decade of life starting with foot dystonia, which 160  
102 progress to involve other body parts, but typically 161  
103 remains more severe in the lower extremities. The 162  
104 severity increases progressively over the first two 163  
105 decades of life, but plateaus with relatively few side 164  
106 effects and no long-term complication [16]. Untreated 165  
107 individuals developed diurnal fluctuations with marked 166  
108 improvement in the morning and worsening in the 167  
109 evening. DRDs are more frequent in female than in 168  
110 males, with a ratio varying from 1 to 4.3:1. Diagnosis of 169  
111 DRD can often be made on clinical grounds [17]. 170  
112 There are reports about DRD induction by diazepam 171  
113 [18], bupropion [19], cetirizine [20], riluzole [21], and 172  
114 tetrabenazine [22]. The authors, however, didn't find 173  
115 any reports about post-lamotrigine conditions. 174  
116 Lamotrigine is a new antiepileptic agent that is 175  
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## 141 REFERENCES

- 142 1. Ropper AH, Brown RH. Adams and Victor's Principles of  
143 Neurology, 8<sup>th</sup> 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, Matsuoka F, Messenheimer JA,  
177 Faught 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, Tavaraschi 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. 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 PA, 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.

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