Valproate-Induced Generalized Choreoathetosis

Alfonso Giordano, MD, PhD,^{1,2} Marianna Amboni, MD, PhD,^{2,3} Alessandro Tessitore, MD, PhD^{1,*}

A 53-year-old white woman with a history of mental retardation and epilepsy complicating a childhood meningitis, well-controlled with chronic phenytoin 250 mg/day, developed two breakthrough generalized tonic-clonic seizures. She had no family history of epilepsy or other neurological diseases. Neurological examination at admission was normal. EEG showed epileptiform activity, and phenytoin blood level was in the therapeutic range (20 mg/L). Valproate (VPA) was added, titrated to 900 mg/day, with seizure remission. After a few days, she developed lethargy and generalized involuntary movements. Neurological examination showed continuous choreoathetotic movements involving head, mouth, lips, tongue, trunk, and lower extremities with dystonic posturing of foot and trunk (see Video, segment 1). Laboratory investigations, including electrolytes (calcium, phosphorus, and magnesium), thyroid function tests, transaminases, and serum ammonia, were all normal; phenytoin and VPA blood levels were within normal ranges (21 and 90 mg/L, respectively), while anti-nuclear and anti-cardiolipin antibodies were negative. No EEG epileptiform activity was detected, and a brain CT scan showed bilateral basal ganglia calcifications (Fig. 1); parathyroid hormone and vitamin D levels were normal, as were serum lactate and pyruvate. Based on the temporal relationship between VPA administration and onset of involuntary movements, VPA was slowly discontinued. This resulted in marked improvement within the first 3 days and complete recovery in 1 week (see Video, segment 2).

Although VPA, a gamma-aminobutyric acid (GABA)ergic antiepileptic drug,¹ is most often associated with drug-induced parkinsonism,² it can induce chorea or choreoathetosis in the setting of pre-existent basal ganglia injury, directly, or along corticostriatal pathways.³ Lancman et al. reported 3 patients who developed subacute chorea during VPA treatment. All patients had pre-existing brain damage: 2 had severe mental retardation resulting from birth complications, and 1 had unilateral caudate lesion after a car accident.³ More recently, reversible hemichorea has been described in a patient on VPA monotherapy with pre-existing right frontal hemorrhage.⁴ Our case is the first report of VPA-induced generalized

Figure 1 Brain CT scan: symmetrical basal ganglia calcifications.

choreoathetosis in a patient with bilateral pallidal calcifications, which can be detected in 0.3% to 1.5% of routine CTs, or can be related to inherited (i.e., mitochondrial diseases or idiopathic basal ganglia calcifications) or sporadic disorders (ischemic, neoplastic, infectious, toxic, or traumatic cerebral insults and metabolic alterations).⁵ In our patient, a negative family history, with the absence of both progressive neurological dysfunction and biochemical abnormalities suggestive of metabolic or mitochondrial disorders, suggests that calcifications may represent a possible sequelae of her childhood meningitis.

In agreement with previous reports, we hypothesize that VPA-induced chorea may be a result of unbalanced GABAergic activity in the presence of pre-existing brain injury.^{3,4} It has been demonstrated that high or toxic serum VPA concentrations, inactivate glutamate decarboxylase, which is the rate-limiting enzyme in the production of GABA and is normally activated by VPA.¹ The resulting GABAergic tone reduction in the basal ganglia-thalamocortical pathways would be expected to overactivate the motor cortex, leading to the subsequent development of a hyperkinetic (i.e., choreoathetosis), rather than hypokinetic (i.e., parkinsonism) complication from VPA administration. Therefore, VPA-induced chorea seems to require both high or toxic VPA serum concentrations and pre-existing brain injury. This case report highlights the impor-

¹Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Second University of Naples, Naples, Italy; ²IDC Hermitage Capodimonte, Naples, Italy; ³Department of Neurological Sciences, University of Naples "Federico II", Naples, Italy

*Correspondence to: Dr. Alessandro Tessitore, Department of Neurology, Second University of Naples, Piazza Miraglia 2, 80100 Naples, Italy; E-mail: alessandro.tessitore@unina2.it

Keywords: valproate disease, choreoathetosis, basal ganglia calcifications.

Relevant disclosures and conflicts of interest are listed at the end of this article.

Received 29 April 2014; revised 9 June 2014; accepted 12 June 2014.

Published online 28 July 2014 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12069

tance of an accurate pharmacological history when approaching a patient with subacute onset of movement disorders because of the potential for recovery upon drug discontinuation.⁶ Moreover, the VPA, singly or in combination with phenytoin or carbamazepine,⁷ should be used with caution in those with pre-existing basal ganglia injury.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique

A.G.: 1A, 3A

M.A.: 3B

A.T.: 1A, 1B, 3B

Disclosures

Funding Sources and Conflicts of Interest: The authors report no sources of funding and no conflicts of interest.

Financial Disclosures for previous 12 months: The authors declare that there are no disclosures to report.

References

1. Loscher W, ed. *Valproate*. Basel Switzerland: Birkhauser Verlag; 1999: 22.
2. Zadikoff C, Munhoz RP, Asante AN, Politzer N, Wennberg R, Carlen P, Lang A. Movement disorders in patients taking anticonvulsants. *J Neurol Neurosurg Psychiatry* 2007;78:147–151.
3. Lancman ME, Asconapé JJ, Penry JK. Choreiform movements associated with the use of valproate. *Arch Neurol* 1994;51:702–704.
4. Srinivasan S, Lok AW. Valproate-induced reversible hemichorea. *Mov Disord* 2010;25:1511–1512.
5. Bonazza S, La Morgia C, Martinelli P, Capellari S. Strio-pallido-dentate calcinosis: a diagnostic approach in adult patients. *Neurol Sci* 2011;32:537–545.
6. Robottom BJ, Shulman LM, Weiner WJ. Drug-induced movement disorders: emergencies and management. *Neurol Clin* 2012;30:309–320.
7. Gunal DI, Guleryuz M, Bingol CA. Reversible valproate-induced choreiform movements. *Seizure* 2002;11:205–206.

Supporting Information

A video accompanying this article is available in the supporting information here.

Video. Segment 1: Lethargy and generalized choreoathetotic movements with dystonic posturing of feet and trunk. Segment 2: VPA discontinuation: progressive improvement and complete recovery in 1 week.