Background: Myoclonus can occur in association with lithium therapy at toxic and therapeutic dosages, and can be a predominant and disabling adverse effect. Moreover, myoclonus has been reported when lithium has been combined with cyclic antidepressants and with the neuroleptic clozapine. Although clinical case reports exist, no electrophysiologic data are available that provide a source or a neurophysiological mechanism for the myoclonus seen in lithium therapy.

Objective: To describe the electrophysiologic characteristics and source of the myoclonus associated with lithium therapy.

Design and Methods: We retrospectively analyzed 5 cases of myoclonus during lithium therapy. We reviewed the clinical features and results of previous electrophysiologic testing. Four patients received lithium monotherapy; and 1, sertraline hydrochloride and nefazodone hydrochloride in addition to lithium. The electrophysiologic data that had been gathered included multichannel surface electromyographic (EMG) recordings with simultaneous electroencephalography (EEG), somatosensory evoked potentials, and elicitation of long-latency EMG reflexes to median and digital nerve stimulation.

Results: All 5 patients showed multifocal action myoclonus without reflex activation and only rare occurrence at rest. In each case, back-averaging created a focal EEG transient over the contralateral sensorimotor area preceding the myoclonus EMG discharge. In 2 of the patients receiving lithium monotherapy, the therapy was discontinued and the myoclonus disappeared.

Conclusions: Lithium, by itself, can be associated with prominent clinical myoclonus, short-duration (<50-millisecond) myoclonus EMG discharges and cortical action myoclonus without the presence of epileptiform abnormalities on the routine EEG. This myoclonus is different from the most common form that is well documented to occur with tricyclic antidepressant therapy by clinical and electrophysiologic means.

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M yoclonus can occur in association with lithium therapy at toxic and therapeutic dosages, and can be a predominant and disabling adverse effect. Moreover, myoclonus has been reported when lithium has been combined with cyclic antidepressants and the neuroleptic clozapine. Although clinical case reports exist, electrophysiologic data that would provide insight into the classification and neurophysiological features of lithium-induced myoclonus are not available. Electroencephalographic (EEG) abnormalities have been shown to be consistently present in lithium toxic effects associated with mental status changes. These changes may include slowing of the normal alpha rhythm, paroxysmal and/or persistent slow waves, and epileptiform discharges. Some correlation exists with the lithium level and the clinical state, but time lags between clinical events and the EEG commonly occur. Lithium-induced generalized seizures are usually associated with an abnormal EEG finding. However, lithium-induced myoclonus has not been reported to correlate closely with any type of gross EEG abnormality or other signs of clinical toxicity. Recently, we reported a case of myoclonus in a patient who was being treated with lithium and doxepin hydrochloride. This patient’s electrophysiologic characteristics suggested a cortical origin of the associated myoclonus. The purpose of the present study is to report the electrophysiologic findings on a retrospective series of patients with lithium-induced myoclonus to develop a hypothesis about classification and neurophysiological features of this phenomenon.

METHODS

We retrospectively analyzed all of the cases of myoclonus examined in our movement disorders laboratory in association with lithium treat-
Clinical and Electrophysiologic Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Medications*</th>
<th>Lithium Level, mEq/L†</th>
<th>EEG Background, Hz</th>
<th>Latency From Back-Averaged Transient to Myoclonus, ms</th>
<th>SSEP Cortical Wave Amplitude, Right/Left, µV‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lithium, 600 mg BID</td>
<td>ND</td>
<td>10.0</td>
<td>17</td>
<td>ND/ND</td>
</tr>
<tr>
<td>2</td>
<td>Lithium, 300 mg BID</td>
<td>ND</td>
<td>12.0</td>
<td>20</td>
<td>ND/ND</td>
</tr>
<tr>
<td>3</td>
<td>First study—lithium, 300 mg BID</td>
<td>1.2</td>
<td>10.0 With paroxysmal theta</td>
<td>16</td>
<td>ND/5.9/ND</td>
</tr>
<tr>
<td></td>
<td>Second study—none</td>
<td>ND</td>
<td>10.0</td>
<td>Myoclonus not present</td>
<td>4.3/6.0/6.2/12.4</td>
</tr>
<tr>
<td>4</td>
<td>First study—lithium, 900 mg alternating with 1200 mg OD; propranolol hydrochloride, 20 mg TID</td>
<td>1.4</td>
<td>9.0 With paroxysmal theta</td>
<td>10</td>
<td>7.2/ND/7.0/ND</td>
</tr>
<tr>
<td></td>
<td>Second study—same except lithium therapy discontinued</td>
<td>ND</td>
<td>11.0</td>
<td>Myoclonus not present</td>
<td>6.5/2.0/3.7/1.9</td>
</tr>
<tr>
<td>5</td>
<td>First study—lithium, 300 mg BID; nefazodone hydrochloride, 200 mg BID; sertraline hydrochloride, 100 mg OD</td>
<td>0.5</td>
<td>8.0 With paroxysmal theta</td>
<td>25</td>
<td>3.8/1.0/0.7/0.2</td>
</tr>
<tr>
<td></td>
<td>Second study—same except nefazodone therapy discontinued</td>
<td>ND</td>
<td>8.0 With paroxysmal theta</td>
<td>Too few myoclonus discharges to back-average</td>
<td>4.0/1.0/0.2/0.16</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice per day; EEG, electroencephalography; ND, not done; QD, once per day; QWK, once per week; SSEP, somatosensory evoked potential; TID, 3 times per day.

*Includes only those thought to be psychoactive or that could affect cortical function. Lithium was given as lithium carbonate.
†The therapeutic laboratory range for lithium is 0.8 to 1.2 mEq/L.
‡Elevated values for SSEPs N20-P25 are >9.7; for P25-N33, >11.1.

Five cases of myoclonus in the context of lithium therapy were evaluated from January 1, 1996, through December 31, 2001 (Table). They included 3 women and 2 men, with ages ranging from 42 to 72 years. Four of these patients were receiving lithium monotherapy at the time of evaluation (patients 1-4), and 1 was receiving lithium, sertraline hydrochloride, and nefazodone hydrochloride (patient 5). Patients 1 and 2 were being treated for severe depression, and patients 3 through 5 were being treated for bipolar disorder. All patients were referred to our movement disorders clinic for assessment of their hyperkinetic movement disorder. In all patients, arm movement precipitated multifocal action myoclonus, and myoclonus rarely occurred at rest. Reflex activation of the myoclonus was not present for touch, stretch, deep tendon reflexes, light, sound, or startle in any patient. In all cases, the results of the neurological examination were unremarkable except for the myoclonus. In particular, no ataxia or mental status abnormalities were found. This action myoclonus was disabling and represented the chief complaint for these patients. No other clinical signs of lithium toxicity were noted.

All patients showed less than 50-millisecond EMG discharges correlating with the multifocal myoclonic jerks in the upper extremities, often with cocontraction of agonistic, antagonistic, and occasionally contiguous muscle segments. The myoclonus EMG discharges were back-averaged using the right wrist extensors in 3 patients and the right deltoid in 2 patients. The back-averaging created a focal EEG transient over the contralateral sensorimotor area. These transients had a similar appearance for all 5 patients. No other clinical signs of lithium toxicity were noted.

In patients 3 and 4, clinical assessment and the electrophysiologic study were repeated approximately 3 weeks after the discontinuation of the lithium therapy. For both patients, the myoclonus disappeared. Data from patient 4
are shown in Figure 1 and Figure 2. In patient 5, after withdrawal of nefazodone therapy, the myoclonus showed marked clinical and electrophysiologic improvement. However, not enough myoclonus EMG discharges were available to perform back-averaging. Patients 1, 2, and 5 decided to continue lithium therapy, despite being told that the lithium was responsible for their myoclonus.

COMMENT

These results clearly show that lithium by itself can be associated with cortical action myoclonus without the presence of epileptiform abnormalities on the routine EEG. The presence of a focal back-averaged EEG transient before the myoclonus represents good evidence of a cortical origin of the myoclonus. The evaluation results in patients 3 and 4 before and after lithium monotherapy provide strong evidence of the correlation of lithium monotherapy with myoclonus. After lithium therapy withdrawal, both patients showed improvements in the EEG background rhythm. Of the 3 patients in whom lithium levels were obtained, only one had a lithium level above the laboratory therapeutic range while experiencing myoclonus, and another had a low serum value but with a good clinical response. Patient 5 had myoclonus while taking lithium, sertraline, and nefazodone. After discontinuation of the nefazodone therapy, the myoclonus was greatly reduced and no longer bothersome to the patient. Although it is not possible to conclude that lithium was the only agent causing myoclonus in this patient, it is obvious that nefazodone significantly exacerbated the myoclonus. Moreover, the myoclonus was of cortical origin, with similar electrophysiologic features to those of the patients receiving lithium monotherapy. In the past, the mechanism of lithium-induced myoclonus has been ascribed to the facilitation of presynaptic serotonin release. Nefazodone inhibits the uptake of serotonin and norepinephrine. Thus, in patient 5, further augmentation of serotonin activity by nefazodone might have exacerbated the relatively mild lithium- and/or sertraline-induced myoclonus. These data suggest a role for serotonin augmentation in the production of cortical action myoclonus in patients taking lithium and other psychostimulants. We hypothesize that serotonin augmentation at the cortical level is critical to the production of the lithium-induced myoclonus discharges that arise from the sensorimotor cortex. Although serotoninergic influences may also indirectly contribute to cortical hyperexcitability from other sites, the focal discharges recorded in our subjects suggest direct cortical modulation. A guinea pig model of myoclonus has implicated serotonin type 1 and 2 receptors in the mediation of serotonin-induced myoclonus. Serotonin type 1 and 2 receptors are present in cortical areas, among other regions, and serotonin type 2A receptors have their highest density at the neocortex. In the rodent brain, receptor-mediated serotoninergic effects can be excitatory or inhibitory on pyramidal cells and interneurons. Thus, excessive serotonin augmentation could produce sensorimotor cortical discharges responsible for myoclonus.

Patient 3 had an enlarged SSEP, which is a common association in cortical myoclonus. In the 2 patients who had SSEPs obtained before and after discontinuation of lithium therapy, the P25-N33 amplitude was reduced, which suggests a decrease in sensory cortex excitability. Our results, in combination with those of the EEG literature, suggest that a spectrum of lithium-induced electrophysiologic abnormalities may exist that are associated with different clinical manifestations of motor cortex hyperexcitability. At therapeutic levels or levels of mild lithium toxicity, isolated action myoclonus can be associated with background rhythm changes, back-averaged cortical myoclonus transients, and increased sensory cortical excitability. Instances of greater lithium toxicity can demonstrate motor seizures and/or generalized convulsions. Such cases usually occur with more impressive EEG paroxysmal slow waves and, in some instances, interictal epileptiform abnormalities. Obeso et al have described such a concept as a “spectrum of cortical myoclonus.”

This myoclonus is different from the most common form of myoclonus that is well documented to occur with tricyclic antidepressants by clinical and electrophysiologic means. Garvey and Tollefson reported 39 cases of myoclonus due to cyclic antidepressants. In their series, the myoclonus occurred at rest and was disabling in only 23% of those who reported it. Our patients had action myoclonus that was uniformly disabling through dysfunctional limb control, and myoclonus occurred rarely at rest. Thus, one can easily differentiate between these 2 types of myoclonus on a clinical basis. Forstl and Pohlmann-Eden found enlarged N20-P25 SSEP waves in 2 patients with myoclonus at rest induced by cyclic anti-
pressants. None of our patients had enlarged N20-P25 SSEP waves. Only 1 of our patients demonstrated an enlarged P25-N33 SSEP wave. When the cortical SSEP is enlarged, the P25-N33 wave is the typical SSEP enlargement that occurs in patients with action myoclonus. More electrophysiologic studies that evaluate the effects of various psychoactive drugs need to be conducted, but our results and those of a few studies suggest that electrophysiologic and clinical characteristics may sometimes differentiate between the myoclonus seen in lithium treatment vs cyclic antidepressant treatment alone.

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Author contributions: Study concept and design (Dr Caviness); acquisition of data (Drs Caviness and Evidente); analysis and interpretation of data (Drs Caviness and Evidente); drafting of the manuscript (Drs Caviness and Evidente); critical revision of the manuscript for important intellectual content (Drs Caviness and Evidente).

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REFERENCES


Figure 2. Electroencephalography-electromyography (EEG-EMG) back-averaging. The EEG transient back-averaged from 100 myoclonus EMG discharges during EEG-EMG polygraphy in patient 4. The back-averaging created a focal EEG transient over the contralateral sensorimotor area that preceded the myoclonus.