Diazepam for outpatient treatment of nonconvulsive status epilepticus in pediatric patients with Angelman syndrome

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ABSTRACT

Nonconvulsive status epilepticus (NCSE) is present in multiple pediatric neurogenetic syndromes with epileptic encephalopathies. While intravenous (IV) medications are used inpatient for treatment of critical illness–related NCSE, there is no consensus on treatment of ambulatory NCSE. Up to 50% of patients with Angelman syndrome (AS) have NCSE with myoclonic or atypical absence status. Here we report our experience in pediatric patients with AS and NCSE treated outpatient with a tapering course of oral diazepam. We conducted a chart review of 104 patients seen in the Angelman Syndrome Clinic at Massachusetts General Hospital from January 2008 to March 2017, who met the criteria. Response to treatment was defined as cessation of NCSE symptoms with electroencephalogram (EEG) confirmation when possible. Twenty-one patients with NCSE were identified, and 13 patients (9 male) with 25 episodes of NCSE were included. Mean age at NCSE episode was 5 years 4 months (15 months–12 years). Six patients had one episode of NCSE, and 7 patients had recurrent episodes (mean: 2.7; range: 2–4). Median diazepam treatment was 6 days (4–12 days), with a mean dose of 0.32 mg/kg/day divided over 2–3 administrations, decreased every 2 days. Nine episodes required multiple courses; however, oral diazepam alone was ultimately successful in 80% (20/25) of NCSE episodes. Oral diazepam was well-tolerated with no major side effects. A short course of oral diazepam is well-tolerated and effective in patients with AS who have ambulatory NCSE. It may be considered prior to escalating to inpatient care in AS and possibly other epilepsy syndromes.

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1. Introduction

Nonconvulsive status epilepticus (NCSE) was first described in modern times by W.G. Lennox in patients with chronic epilepsy in 1945 [1], though there is historical evidence of a case description as early as the year 1501 [2]. While initially described in ambulatory patients, NCSE has been increasingly recognized in the critical care setting in patients with encephalopathy. Overall population incidence is estimated at 5.6 to 18.3 per 100,000 persons per year [3]. There is no universally accepted definition for NCSE. One of the most common definitions is a condition of prolonged electrographic seizure activity without convulsions resulting in nonconvulsive clinical symptoms [3]. Many use 30 min of epileptic activity as an operational definition for NCSE in studies, though the time frame is arbitrary. Nonconvulsive status epilepticus was previously divided into complex partial status epilepticus or absence status epilepticus based on focal or generalized discharges. Some groups advocate for differentiating ambulatory or “proper” NCSE from NCSE that occurs in the setting of coma [4,5]; other groups advocate classification of NCSE by etiology, separating those associated with chronic conditions such as epilepsy or neurodegenerative disorders from those associated with acute conditions such as postcardiac arrest, traumatic brain injury, or encephalitis as the morbidity and mortality differ significantly [6]. While there are many iterations of NCSE classification schemes, there is a clear difference in those that are epilepsy-related in the ambulatory setting. In ambulatory patients with NCSE, a preexisting diagnosis of epilepsy is present in 62% of patients, compared with 6% of patients who are comatose or in critical care settings; inversely, mortality is 3–6% for epilepsy-related ambulatory NCSE vs. 27–61% for critical care NCSE in adults [5,7].

While the NCSE literature had been dominated by a relatively recent explosion of critical illness-related NCSE, 50% of NCSE cases occur in patients with epilepsy [3]. Nonconvulsive status epilepticus occurs with increased frequency in certain pediatric genetic epilepsy syndromes or epileptic encephalopathies such as the following: approximately 50% of patients with Angelman syndrome (AS) [8–14], 40% of patients with Dravet syndrome [15,16], 75–85% of patients with Lennox–Gastaut [15,17], and almost all children with Ring Chromosome 20 syndrome [3,18]. Even benign childhood epilepsy syndromes are...
Table 1
Clinical and EEG findings of patients.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>AS subtype</th>
<th>Age</th>
<th>Clinical presentation</th>
<th>Trigger</th>
<th>EEG findings with % of EEG with epileptiform discharges</th>
<th>Seizure treatment</th>
<th>Treatment</th>
<th>2nd course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Deletion</td>
<td>1 year 3 months</td>
<td>Somnolent, tremors, decreased social interaction</td>
<td>Recent viral illness and new seizure</td>
<td>–</td>
<td>LGIT</td>
<td>DZP 6 day taper starting at 0.22 mg/kg/day divided BID</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 year 4 months</td>
<td>Somnolent, decreased social interaction</td>
<td>Recent viral illness and new seizure</td>
<td>–</td>
<td>LGIT</td>
<td>DZP 9 day taper starting at 0.3 mg/kg/day divided BID</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 year 11 months</td>
<td>Fatigue</td>
<td>Worsening GI dysfunction</td>
<td>&lt;50%, 700 μV frontally predominant spike and wave at 1–2.5 Hz</td>
<td>LGIT</td>
<td>DZP 6 day taper starting at 0.26 mg/kg/day divided BID</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 year 8 months</td>
<td>Atonic seizures</td>
<td>Viral illness</td>
<td>–</td>
<td>LGIT</td>
<td>DZP 6 day taper starting at 0.26 mg/kg/day divided BID</td>
<td>Y</td>
</tr>
</tbody>
</table>

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