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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.

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

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Table 1
Clinical and EEG findings of patients.

Pt	Sex	AS subtype	Age	Clinical presentation	Trigger	EEG findings with % of EEG with epileptiform discharges	Seizure treatment	Treatment	2nd course
1	M	Deletion	1 year 3 months	Somnolent, tremors, decreased social interaction	Recent viral illness and new seizure	–	LGIT	DZP 6 day taper starting at 0.22 mg/kg/day divided BID	N
			1 year 4 months	Somnolent, decreased social interaction	Recent viral illness and new seizure	95%, 700 μV frontally predominant generalized spike and wave at 1–2.5 Hz	LGIT	DZP 9 day taper starting at 0.3 mg/kg/day divided BID	N
			1 year 11 months	Fatigue	Worsening GI dysfunction	50%, 700 μV frontally predominant generalized spike and wave at 2–2.5 Hz	LGIT	DZP 6 day taper starting at 0.26 mg/kg/day divided BID	Y[a]
			1 year 8 months	Atonic seizures	Viral illness	–	LGIT	DZP 6 day taper starting at 0.26 mg/kg/day divided BID Added CLB	Y
2	M	Deletion	1 year 6 months	Pallor, increased drooling, "not himself"	Carnival trip	–	LEV	DZP 9 day taper starting at 0.29 mg/kg/day divided BID Increased LEV	Y
			2 years 7 months	Motor regression, increased seizure frequency, fatigue	–	>50%, high amplitude frontally predominant generalized spike and wave at 1–1.5 Hz[c]	LEV	DZP 6 day taper starting at 0.57 mg/kg/day divided TID	N
3	M	Deletion	2 years 11 months	Prolonged postictal period after multiple GTCs	–	80%, 600 μV generalized spike–wave discharges	–	DZP 9 day taper starting at 0.38 mg/kg/day divided BID Added LEV	N
4	M	Deletion	3 years 4 months	Somnolent, motor regression, poor sleep, decreased communication, atonic seizures, increased myoclonus	–	>95%, 750 μV frontally predominant generalized spike and slow wave discharges at 1.5–2 Hz	–	DZP 6 day taper starting at 0.25 mg/kg/day divided BID	N
			3 years 8 months	Appeared "off", dry heaving, myoclonus	–	>90%, 800 μV frontally predominant generalized spike and slow wave discharges at 1.5–2 Hz	–	DZP 12 day taper starting at 0.38 mg/kg/day divided BID Transitioned gluten-free, casein-free diet to LGIT	Y
5	F	Deletion	4 years 2 months	Fatigue, staring episodes, motor regression, myoclonus	Sleep problems, gastrointestinal illness	"Frequent bursts of generalized spike and slow wave activity"[c]	CLB, VPA	DZP 6 day taper starting at 0.45 mg/kg/day divided BID Added LEV and RFM	Y
			5 years 4 months	Staring frequently, myoclonus, increased seizure frequency	Tooth infection	70%, 700 μV generalized spike and wave discharges at 2–2.5 Hz	CLB	DZP 8 day taper starting at 0.44 mg/kg/day divided TID Increased CLB	N[b]
			5 years 10 months	Somnolent, developmental regression	Aspiration pneumonia	–	CLB, LTG	DZP 8 day taper starting at 0.44 mg/kg/day divided TID	N
			6 years 4 months	"Behavioral changes" and drop seizures	Decreased CLB dose	–	CLB, LTG	DZP 4 day taper starting at 0.18 mg/kg/day divided BID Increased CLB	Y[b]
6	M	Deletion	4 years 4 months	Fatigue, constipation	–	90%, 1000 μV left frontal predominant generalized spike and slow wave at 1.5–2 Hz	CLB, LEV, LGIT	DZP 6 day taper starting at 0.24 mg/kg/day divided BID	N
			6 years 1 month	Sleep disturbance	LEV wean	–	CLB, LEV	DZP 6 day taper starting at 0.36 mg/kg/day divided TID Restarted LGIT	N
			7 years 8 months	Developmental regression, loss of motor skills, poor balance	Allergies	50%, 650 μV generalized spike and slow wave discharges at 2–2.5 Hz	CLB, LEV, LGIT	DZP 6 day taper starting at 0.23 mg/kg/day divided TID Increased CLB and LEV	N
7	M	Deletion	6 years 0 months	Increased absence seizures	Poor sleep, constipation	–	LEV, LGIT, VPA	DZP 6 day taper starting at 0.2 mg/kg/day divided BID Halved carbohydrate allowance of LGIT	N
			6 years 11 months	Fatigue, malaise, poor balance, decreased social interactions and communication	Recent sinus infection	80%, 3 Hz generalized spike and wave activity	LEV, LGIT, VPA	DZP 6 day taper starting at 0.4 mg/kg/day divided BID Increased LEV dose and halved carbohydrate allowance of LGIT	Y
8	M	Deletion	7 years 1 month	Decreased alertness, increased seizure frequency	–	>95% frontally predominant generalized spike and wave discharges at 1–2 Hz	LCM, LEV, TPM	DZP 6 day taper starting at 0.42 mg/kg/day divided BID	Y[b]
			8 years 9 months	Fatigue, increased seizure frequency	–	>95%, 1000 μV generalized spike and wave discharges at 1.5–2 Hz	DZP, LEV, LTG, VPA	DZP 4 day taper starting at 0.36 mg/kg/day divided BID Increased baseline DZP dose after taper	Y[b]
9	F	Deletion	7 years 4 months	Decreased activity, increased seizure frequency, falling	–	50–60%, 700 μV generalized frontally predominant spike and wave discharges at 2.5–3 Hz	CLB, LTG	DZP 12 day taper starting at 0.38 mg/kg/day divided TID Increased LTG dose	N[b]

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