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Growth and endocrine function in children with Dravet syndrome

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ABSTRACT

Purpose: Dravet syndrome is an intractable childhood epilepsy syndrome most often associated with an *SCN1A* mutation. In our clinical practice, several patients with Dravet syndrome were noted to have short stature and endocrine dysfunction. This has not been reported in the literature. Our study aim was to describe growth measurements and endocrine abnormalities in children with Dravet syndrome.
Method: A retrospective chart review was performed at a single institution. Eligibility criteria included clinical and genetic (*SCN1A*) diagnosis of Dravet syndrome. Records were reviewed for height and weight measurements and serologic evidence of endocrine abnormality, as well as patient demographics, anti-seizure medication, and family history. Age and gender specific trend of height and weight measurements, using z-scores, were compared to CDC growth curves (Centers for Disease Control and Prevention [1]).
Results: Sixty-eight children were identified, 46% male, age 1–21 years, taking an average of 2.9 anti-seizure medications per patient. Mean growth parameter measurements were significant for decrease in height z-score of 0.10 ($p = < 0.001$) and decrease in weight z-score of 0.09 ($p = < 0.01$) for every year increase in age, such that with increasing age the cohort moved farther away from the mean. The average group height and weight z-score, at age 8, was −0.45 and −0.09, respectively. After adjusting for age, neither gender, family history, or anti-seizure medication was associated with height or weight z-score. Serologic endocrine results were available for 26 children (38%). This identified low insulin-like growth factor 1 (IGF-1) in 7/15 and low testosterone in 2/10. Two children received growth hormone supplementation. TSH testing was abnormal <10% of the time.
Conclusions: Comorbidities in children with Dravet syndrome may involve more systems than previously reported. We report a cohort of children with Dravet syndrome with reduced height and weight growth trend, as well as a subset with endocrine dysfunction evidenced by low IGF-1 and testosterone levels. Additional prospective research is needed to further define the significance of this relationship.
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1. Introduction

Dravet syndrome (also known as severe myoclonic epilepsy of infancy) is an intractable childhood epileptic encephalopathy with onset in the first year of life. The incidence of Dravet syndrome was initially estimated at 1 in 30,000–40,000 live births [2,3], although data from a California-based population identified an incidence of 1 per 15,000–20,000 [4]. In most cases, Dravet syndrome is caused by *de novo* mutations of the *SCN1A* gene that encodes for the alpha-subunit of the neuronal voltage-gated sodium channel [5]. *SCN1A* gene mutations are found in 70–90% of patients with a clinical diagnosis of Dravet syndrome [4,6].

Children with Dravet syndrome are healthy and have normal development prior to seizure onset [7]. Seizures often start within the first year of life and are characterized by frequent and prolonged febrile seizures that are often hemiclonic. Multiple seizure types can occur over time, including atypical absence, myoclonic, generalized tonic clonic, and focal onset seizures. EEG findings are initially normal but with time background slowing and focal or generalized and polyspike wave discharges appear, which may persist into adulthood [8].

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Other features of Dravet syndrome have been described including neurocognitive decline and ataxia [7,9]. Behavioral disturbances with hyperactivity and autistic features are often present during early childhood [10]. Studies into adulthood have identified motor abnormalities and impaired walking, as well as cerebellar features such as ataxia, dysarthria, intention tremor, and eye movement disorders [8]. Prior descriptions of children with Dravet syndrome and their phenotype are available in the literature and have not reported endocrine or growth abnormalities.

Little is known of the exact relationship between endocrine abnormalities and epilepsy, especially in children. In adult literature, endocrine abnormalities have been reported in 20–25% of women with temporal lobe epilepsy prior to treatment with anti-seizure medication [11]. A small case control study of children with both focal onset and idiopathic generalized epilepsy treated with carbamazepine or valproate monotherapy found epilepsy patients to have reduced linear growth as compared to controls, but with normal IGF-1 testing [12]. Other studies of children with epilepsy have reported normal linear growth [13,14]. There is more known about the effect of anti-seizure medications on endocrine function. Anti-seizure medications themselves (valproate, phenobarbital, carbamazepine) can be associated with endocrine dysfunction, including short stature, increased testosterone levels, and thyroid dysfunction [15,16]. Furthermore, there is concern that the ketogenic diet can also lead to poor growth long-term but again the evidence is inconsistent.

In the literature, there is no report of growth abnormalities or endocrine dysfunction in children with Dravet syndrome, although clinically we have noted short stature and weight concerns, as well as abnormal endocrine labs in several of our patients with Dravet syndrome. The aim of the current study is to evaluate growth parameters and characterize endocrine abnormalities in children with Dravet syndrome.

2. Methods

A retrospective chart review was performed at Children's Hospital of Colorado from September 1999 until May 2015. Children were identified from a clinical database of Dravet syndrome patients and also by interrogation of the electronic medical record for the diagnosis of Dravet syndrome or *SCN1A* gene mutation. Eligibility criteria included both a clinical diagnosis of Dravet syndrome and positive *SCN1A* genetic testing. *SCN1A* variants of unknown significance were included if there was a clinical presentation consistent with Dravet syndrome. Parental report of positive *SCN1A* genetic testing was allowed if prior records were not available. Patients with a clinical diagnosis of Dravet syndrome without confirmatory genetic testing were excluded. Study data were collected and managed using REDCap electronic data capture tools hosted at University of Colorado Denver [17]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Records were reviewed for height and weight measurements and serologic evidence of endocrine abnormality, including growth hormone, sex hormones, cortisol, and thyroid testing, as well as for demographic information, current anti-epileptic medication, and family history of endocrine disease.

All available growth measurements (height and weight) for the entire study cohort of 68 patients were downloaded from our electronic medical record (EPIC). The growth parameters of children between the ages of 2 and 19 were included in the height and weight analyses and compared to CDC 2000 growth curves [1,18]. Growth measurements taken at an age of less than two years old were excluded as caloric intake and nutritional status, as well as social factors, are key determinants of growth at this age, and less likely underlying genetic potential. By the time children are 18–24 months old they tend to be closer to their genetically predetermined percentile [19]. Single individuals may have had multiple height and weight measurements captured over time. Differences in the same week were considered measurement error, so measures taken in the same week were averaged. Height and weight measurements that changed by more than 5% and 10%, respectively, or were determined to be biologically implausible values (BIV), were examined and removed if deemed to be data entry errors (n = 7). All measurements after initiation of hormonal treatment (testosterone or growth hormone) were excluded from the analysis.

Age and gender-specific height and weight z-scores are calculated from the CDC 2000 growth charts [1]. A z-score represents the difference from the CDC reference population and is expressed in standard deviations from the mean. Multiple measures on a single subject were considered in the analysis. In order to analyze the trend of height and weight (in z-scores) of children with Dravet syndrome as age increases, a linear mixed regression model with a random intercept and slope (age) with an unstructured covariance structure was used. The linearity of age was examined by plotting cubic splines, as well as various loess curves [20]. The Akaike's Information Criteria (AIC) was used to determine model fit. All analyses were performed using Statistical Analysis Systems (SAS Institute, Cary, NC, ver. 9.4)

Serologic endocrine results were available for only a subset of patients in the study cohort. Screening endocrine testing was often ordered by the child neurologist due to growth concerns with referral to an endocrinologist if testing was abnormal. Not all children with poor growth had endocrine testing available. Endocrine results outside of the age based normal range, as defined by the testing laboratory, were considered abnormal. These results are presented in frequencies and percent using descriptive statistics.

3. Results

There were 68 records that met eligibility criteria. The cohort consisted of 46% males, with a median age of 9 years (range 1–21), currently taking an average of 2.9 anti-seizure medications per

Table 1
Cohort characteristics.

Total number of subjects	**68**
Serologic endocrine testing (n)	38% (26)
Growth measurements (n)	94% (64)
Age at time of data extraction (years) – median (range)	9 (1–21)
Male	46%
Hispanic or Latino	18%
Race	
White	72%
Black or African American	4%
Other	24%
Health Insurance[a]	
Medicaid/CICP	84%
Private	38%
Tricare	4%
Current anti-seizure medications	
0–2	36%
≥3–7	63%
Current ketogenic diet	12%
History of ketogenic diet	32%

[a] Total is greater than 100% due to inclusion of secondary insurance.

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