International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	TEN-YEAR KETOGENIC DIET AS PRIMARY THERAPY IN SCN2A-RELATED DRUG-RESISTANT DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY: LONG-TERM EFFICACY, SAFETY, AND MULTISYSTEM OUTCOMES
DOI	https://doi.org/10.31435/ijitss.3(51).2026.6479
RECEIVED	09 May 2026
ACCEPTED	07 August 2026
PUBLISHED	11 August 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

TEN-YEAR KETOGENIC DIET AS PRIMARY THERAPY IN SCN2A-RELATED DRUG-RESISTANT DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY: LONG-TERM EFFICACY, SAFETY, AND MULTISYSTEM OUTCOMES

Bartosz Wójtowicz *(Corresponding Author, Email: bartek.wojtowicz.2002@gmail.com)*
Student Scientific Club of Pediatric Neurology, Medical University of Lublin, Lublin, Poland
ORCID ID: 0000-0002-7396-9117

Szymon Skrzypek
Student Scientific Club of Pediatric Neurology, Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0009-9174-7786

Oliwia Żmuda
Student Scientific Club of Pediatric Neurology, Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0005-0415-786X

Jakub Jasionka
Student Scientific Club of Pediatric Neurology, Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0003-7359-5199

Jagoda Niczyporuk
Student Scientific Club of Pediatric Neurology, Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0003-2035-5650

Patrycja Okoń
Student Scientific Club of Pediatric Neurology, Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0007-0988-5465

Jan Lejman
Department of Child Neurology, Medical University of Lublin, Chodzki 2, 20-093 Lublin, Poland
ORCID ID: 0000-0002-8065-2839

Magdalena Chrościńska-Krawczyk
Department of Child Neurology, Medical University of Lublin, Chodzki 2, 20-093 Lublin, Poland
ORCID ID: 0000-0001-8121-6580

ABSTRACT

Objective: This case study reports a decade-long (2016–2026) follow-up of a girl with gene-confirmed SCN2A-related developmental and epileptic encephalopathy (DEE) in whom the ketogenic diet (KD) was used as primary therapy after failure of eight sequential antiseizure regimens.
Methods: Retrospective analysis of hospital records (2013–2026) covering perinatal history, genetic diagnosis, drug therapy, dietary protocol modifications, and serial laboratory, imaging, and electrophysiological surveillance.
Results: Classic KD initiated at age 2 years 9 months produced rapid seizure reduction (>50%), enabling complete withdrawal of all conventional ASMs by February 2017. The diet was maintained continuously for over 10 years, including through emergency craniotomy for traumatic intracranial hemorrhage in April 2018. Adjunctive CBD/THC oil was used from 2017, with a transient valproate retrial in December 2022. Multisystem complications (hypercalciuria, lumbar osteopenia with BMD Z-score −2.7, transient dyslipidemia) were managed with potassium citrate, vitamin D3/calcium supplementation, and dietary ratio adjustments; no nephrolithiasis or KD-attributable cardiac complications occurred. Growth remained within normal range without gastrostomy.
Conclusions: Long-term KD as primary non-pharmacological therapy is feasible and safe in SCN2A-related DEE, permitting complete ASM cessation, provided multidisciplinary metabolic and bone surveillance is maintained.

KEYWORDS

SCN2A; Ketogenic Diet; Developmental and Epileptic Encephalopathy; Drug-Resistant Epilepsy; Long-Term Follow-Up; Pediatric Neurology

CITATION

Bartosz Wójtowicz, Szymon Skrzypek, Oliwia Żmuda, Jakub Jasionka, Jagoda Niczyporuk, Patrycja Okoń, Jan Lejman, Magdalena Chrościńska-Krawczyk. (2026) Ten-Year Ketogenic Diet as Primary Therapy in SCN2A-Related Drug-Resistant Developmental and Epileptic Encephalopathy: Long-Term Efficacy, Safety, and Multisystem Outcomes. *International Journal of Innovative Technologies in Social Science*. 3(51). doi: 10.31435/ijitss.3(51).2026.6479

1. Introduction

Developmental and epileptic encephalopathies (DEEs) represent a heterogeneous group of early-onset neurological disorders characterized by severe refractory seizures and developmental regression [1]. Among the genetic etiologies of DEE, pathogenic variants in the *SCN2A* gene (chromosomal locus 2q24.3), which encodes the alpha subunit of the voltage-gated sodium channel NaV1.2, account for a substantial proportion of early-infantile cases [2,3]. NaV1.2 is essential for initiating and propagating action potentials in unmyelinated axon initial segments of excitatory glutamatergic neurons during early brain development [3,4].

The clinical spectrum of *SCN2A*-related channelopathies is broad, ranging from benign familial neonatal-infantile seizures to severe early-infantile epileptic encephalopathies (such as Ohtahara syndrome or epilepsy of infancy with migrating focal seizures) and autism spectrum disorders without early epilepsy [1,5]. Genotype-phenotype correlations guide therapeutic choices: early-onset cases (<3 months of age) are predominantly mediated by gain-of-function (GoF) mutations resulting in channel hyperexcitability, which typically respond favorably to high-dose sodium channel blockers (SCBs) such as phenytoin, carbamazepine, or lamotrigine [1,3]. Conversely, later-onset cases (≥3 months) frequently involve loss-of-function (LoF) mechanisms where SCBs are ineffective or paradoxical, exacerbating seizure burden [1].

Despite advances in precision medicine, most patients with *SCN2A* DEE remain refractory to multiple rational combinations of antiseizure medications (ASMs) [3]. In refractory pediatric epilepsy, the ketogenic diet (KD) a high-fat, low-carbohydrate, adequate-protein dietary regimen serves as an established non-pharmacological intervention [6,7,8]. Proposed mechanisms of KD include ketone body-mediated enhancement of GABA synthesis, inhibition of the mammalian target of rapamycin (mTOR) pathway, suppression of vesicular glutamate transporters, and direct modulation of ion channels including ATP-sensitive potassium (KATP) channels and sodium channels [9].

While KD efficacy is well-established in specific metabolic disorders (e.g., GLUT1 deficiency, pyruvate dehydrogenase deficiency) and sodium channelopathies like *SCN1A* Dravet syndrome [9,10], clinical evidence regarding KD in *SCN2A*-related DEE remains limited to small case series and short follow-up durations (typically 2–3 years). Data on the feasibility, multisystem safety, and long-term metabolic impacts of decade-long KD therapy in *SCN2A* channelopathies remain sparse.

We report a detailed 10-year retrospective single-case follow-up of a female patient with SCN2A-related drug-resistant DEE treated continuously with KD as primary therapy from age 2 years 9 months to 13 years, achieving complete withdrawal of conventional ASMs, including during complex perioperative and multisystem clinical events.

2. Methodology and Case Presentation

2.1. Patient Information and Perinatal History

The patient is a 13-year-old female (born in 2013 at 34 weeks of gestation via planned Cesarean section for oligohydramnios, with RhD alloimmunization, birth weight 2380 g, Apgar score 10). Hypothyroidism, diagnosed in infancy, was managed with levothyroxine (12.5 µg/day). The obstetric history was notable for the previous multiple gestation (triplets) with early preterm delivery and neonatal deaths of all three infants, followed by a spontaneous miscarriage.

Onset of focal and multifocal seizures occurred on the 4th day of life. Early clinical manifestations included migratory ocular deviation, apnea with cyanosis, focal clonic movements, and cluster tonic spasms (up to 20 episodes per cluster). Early electroencephalography (EEG) revealed burst-suppression and multifocal sharp-wave discharges characteristic of early-onset epileptic encephalopathy.

2.2. Genetic Diagnosis and Early ASM Failure

Targeted genetic panel sequencing performed at age 2 years identified a disease-associated missense mutation in exon 17 of the *SCN2A* gene, confirming a genetic diagnosis of *SCN2A*-related epileptic encephalopathy (ICD-10: G40.4).

Prior to dietary initiation, the patient failed sequential trials of eight conventional anticonvulsant regimens administered at maximal tolerated doses:

1. Phenobarbital (Luminal): Initiated day 4 of life; partial transient response.
2. Sodium Valproate (Convulex): Administered in infancy; ineffective.
3. Vigabatrin (Sabril): Initiated for cluster spasms; no clinical response.
4. Levetiracetam (Keppra): Trialed without seizure control.
5. Nitrazepam: Minimal sedating effect, persistent seizures.
6. Pyridoxine (Vitamin B6): Trialed to rule out pyridoxine-dependent epilepsy; negative response.
7. Adrenocorticotropic Hormone (ACTH / Synacten): Introduced at age 4 months. Achieved temporary reduction in spasm frequency but was complicated by severe steroid-induced adverse effects, including systemic arterial hypertension, sinus tachycardia, and acute hypertrophic left ventricular cardiomyopathy with intraventricular pressure gradient. ACTH was discontinued, requiring multi-drug antihypertensive therapy (captopril, metoprolol, spironolactone, amlodipine).
8. Topiramate (Topamax): Administered at approximately 9 mg/kg/day; withdrawn by the caregivers after about two months without an increase in seizure frequency.

2.3. Initiation and Protocol Modifications of Ketogenic Diet

At age 2 years 9 months (February 2016), the patient was admitted to our pediatric neurology unit for in-patient initiation of a classic ketogenic diet. The diet was introduced under continuous inpatient monitoring for hypoglycemia and metabolic acidosis.

Key milestones of the 10-year dietary trajectory:

February 2016 (Age 2y 9m): Classic KD initiated. Serum beta-hydroxybutyrate (BHB) levels reached up to 6.1 mmol/L. Within the first months, a >50% reduction in seizure frequency was observed.

February 2017 (Age 3y 9m): All conventional ASMs were weaned and discontinued.

Spring 2017: Adjunctive therapy with CBD/THC oil (initially 5 drops/day) was introduced as complementary therapy.

August 2017 – March 2018 (Age 4y): Diet ratio adjusted to 1.75:1 (3 meals/day) to improve compliance and growth velocity.

April 2018 (Age 4y 11m): Emergency admission following accidental head trauma resulting in a left temporoparietal subdural hematoma (57 × 19 × 65 mm) with mild cerebral edema and a left parietal bone fracture, without midline shift. The patient underwent emergency craniotomy and hematoma evacuation. The Ketogenic Diet was successfully maintained throughout the perioperative and postoperative period using enteral tube/oral formulations without loss of ketosis.

July 2019 (Age 6y 2m): Transitioned to a Modified Atkins Diet (MAD) (1000 kcal/day, 4 meals/day, 25 g carbohydrates/day) due to progressive linear growth requirements.

December 2022 (Age 9y 7m): Transient seizure exacerbation prompted a short-term trial of re-introduced Valproate (VPA 20 mg/kg, serum level 50 μg/mL). Due to lack of clear additional benefits and metabolic instability, VPA was subsequently tapered and stopped.

July 2026 (Age 13y 2m): Current follow-up confirms maintenance of a 2:1 ratio KD (1312 kcal/day; lipid 106.8 g, protein 31.8 g, carbohydrate 28.8 g; as recorded in the dietetic chart) with blood BHB level of 2.9 mmol/L, remaining free of all conventional ASMs.

3. Results and Clinical Outcomes

3.1. Clinical Seizure Control and Neurological Status

Seizure response was evaluated using qualitative clinical descriptions and conventional responder categories (worthwhile improvement defined as >50% reduction in seizure frequency), due to the absence of daily parental diary logs:

Pre-KD Baseline (2013–2015): Daily multifocal myoclonic seizures, cluster tonic spasms (up to 20 episodes/cluster), and nocturnal paroxysmal eye deviations.

Post-KD Year 1–5 (2016–2021): Sustained >50% reduction in total seizure burden. The seizure pattern changed to brief nocturnal myoclonic jerks during sleep onset and fatigue.

Current Status (July 2026, Age 13y 2m): Sustained >50% reduction compared with pre-diet baseline. Present seizure semiology consists of brief focal activity arrests with nystagmus and myoclonic limb twitches upon falling asleep.

Profound neurodevelopmental impairment persists, consistent with the natural history of severe *SCN2A* DEE. Current functional assessment indicates non-verbal status, inability to ambulate independently (sits with support; clinically corresponding to Gross Motor Function Classification System [GMFCS] Level IV–V), and communication restricted to facial expressions and vocalizations.

3.2. Somatic Growth and Anthropometric Trajectory

Somatometric measurements tracked over the 10-year follow-up showed stable growth trajectories despite long-term dietary restriction:

Age 3y 7m (12/2016): Weight 12.0 kg, Height 89.5 cm.

Age 5y 4m (09/2018): Weight 15.8 kg (3rd–10th percentile), Height 110.0 cm (25th–50th percentile).

Age 9y 8m (01/2023): Weight 24.5 kg, Height 128.0 cm (measured along spinal curves).

Age 13y 2m (07/2026): Weight 36.0 kg, Height 140.0 cm, BMI 18.37 kg/m² (normal range for age).

3.3. Laboratory and Metabolic Surveillance

Long-term biweekly to semi-annual laboratory monitoring revealed preserved visceral protein synthesis under prophylactic supplementation:

Table 1. Serial laboratory values during long-term ketogenic diet therapy.

Parameter	Baseline / Early KD (2016)	Mid-Term (2019–2023)	Current Follow-up (07/2026)	Reference Range
Blood Beta-hydroxybutyrate (mmol/L)	up to 6.1	2.4 – 6.4	2.9	2.0 – 5.0 (Therapeutic)
Fasting Blood Glucose (mg/dL)	57	71 – 91	70.7	70.0 – 99.0
Total Cholesterol (mg/dL)	184.0	211.0 (elevated)	162.0	< 190.0
LDL-Cholesterol (mg/dL)	112.0	166.0 (elevated)	110.5	< 115.0
HDL-Cholesterol (mg/dL)	48.0	31.6 (decreased)	43.0	> 45.0
Triglycerides (mg/dL)	88.0	115.0	39.8	< 100.0
Serum Albumin (g/dL)	4.20	4.10	4.13	3.80 – 5.40
Serum Urea (mg/dL)	—	—	106	18.0 – 45.0
Blood Ammonia (µmol/L)	38.0	42.0	30.0	11.0 – 51.0
25-OH Vitamin D (ng/mL)	22.4	31.6	18.2 (mild deficiency)	30.0 – 50.0
Hemoglobin (g/dL)	12.4	12.8	13.2	12.0 – 15.0
Platelet Count (×10⁹/L)	245	210	223	150 – 400

3.4. Serial Paraclinical and Organ Safety Evaluations

Systematic multisystem monitoring confirmed the following organ-specific findings:

Cardiovascular System: ACTH-induced left ventricular hypertrophic cardiomyopathy documented in 2013–2014 completely regressed following ACTH cessation. Serial echocardiograms (04/2014, 05/2026) confirmed intact systolic function (EF 63–68.7%, FS 34–36.7%); at the most recent study (05/2026), chamber dimensions were normal (IVSd 6.5 mm, LVPWd 5.6 mm, MAPSE 16.8 mm, TAPSE 18.3 mm), with absence of arrhythmia on Holter EKG.

Renal and Urinary Tract: Chronic hypercalciuria (elevated urinary calcium-to-creatinine ratio up to 2.75) was detected starting in 2016. Oral alkalinization with potassium citrate (Litocid/Citrolit) and low-dose furazydine (Furagin) prophylaxis successfully prevented nephrolithiasis; serial abdominal ultrasonography (2016–2026) showed no renal parenchymal calcifications or stone formation. Voiding cystourethrography (03/2016) excluded vesicoureteral reflux.

Skeletal System: Dual-energy X-ray absorptiometry (DXA) at age 6 years (07/2019) revealed osteopenia with a lumbar spine (L1- L4) BMD Z-score of -2.7. Intensive oral vitamin D3 and calcium supplementation was instituted, with follow-up DXA performed in January 2026.

Gastrointestinal System: Barium swallow contrast study (10/2016) demonstrated normal esophageal motility without mechanical obstruction or active gastroesophageal reflux. Total oral feeding was successfully maintained using blended ketogenic recipes without requiring gastrostomy tube placement.

4. Discussion

To our knowledge, this study documents one of the longest continuous clinical follow-ups (~10.5 years) of a child with gene-confirmed *SCN2A* drug-resistant epileptic encephalopathy treated with the ketogenic diet. The central finding of this 10-year observation is that dietary therapy served as the primary antiepileptic treatment, enabling complete withdrawal of all conventional antiseizure medications for nearly a decade, while maintaining stable seizure control and acceptable long-term multisystem safety.

4.1. Mechanistic Plausibility of KD in SCN2A Channelopathy

Pathogenic variants in *SCN2A* alter NaV1.2 channel gating properties, leading to either enhanced persistent sodium current (gain-of-function) or loss of action potential firing capacity (loss-of-function) [1,3]. In GoF variants, conventional sodium channel blockers (SCBs) are often therapeutic, but in complex or LoF variants, pharmacotherapy frequently fails or causes paradoxical seizure worsening [1,5].

The response to KD in our patient illustrates the pleiotropic, channel-independent anticonvulsant actions of ketone bodies. Polyunsaturated fatty acids (PUFAs) and ketone bodies (beta-hydroxybutyrate and acetoacetate) have been proposed to stabilize neuronal membranes, modulate ion channel conductance (including KATP channels), and influence neurotransmitter handling and cellular energy metabolism [9]. These metabolic actions bypass single-channel pharmacoresistance, which may explain why KD succeeded where eight sequential drug regimens had failed.

4.2. Primary KD Therapy vs. Conventional ASM Polypharmacy

The paradigm of utilizing KD as a primary treatment rather than a late-stage rescue option is gaining traction in pediatric epileptology [6,7]. In our patient, the period after withdrawal of all conventional ASMs in February 2017 was characterized by improved daytime alertness, reduced motor hypotonia, and enhanced social engagement reported by caregivers; temporal attribution of these changes remains uncertain. (...) Our findings suggest that in selecting genetic channelopathies, long-term KD, with adjunctive non-conventional cannabinoids, can provide sustained anti-seizure activity without the chronic neurotoxicity of classic ASMs.

4.3. Role of Adjunctive Cannabidiol (CBD/THC)

In early 2017, low-dose artisanal CBD/THC oil was added to the dietary regimen. Randomized trials and meta-analytic evidence have validated the antiseizure efficacy of purified CBD [11,12]. However, data regarding CBD co-therapy with KD in *SCN2A* encephalopathy remains limited. In our patient, the introduction of CBD coincided with a further reduction in nocturnal myoclonic clusters and improved alertness reported by caregivers, suggesting a possible adjunctive benefit; the attribution remains uncertain given the concurrent dietary adjustments.

4.4. Causal Attribution and Management of Long-Term Complications

A critical requirement of long-term dietary therapy is distinguishing true KD-induced side effects from pre-existing or drug-induced comorbidities [13,14]. In our patient, causal attribution revealed:

1. Cardiomyopathy (Unrelated to KD): Left ventricular hypertrophy was documented as an acute complication of ACTH (Synacten) therapy in 2013–2014. Serial echocardiograms over 10 years of KD confirmed complete structural recovery and normal ejection fraction (EF 63–68.7%), excluding KD-related selenium-deficient cardiomyopathy [15].

2. Hypercalciuria and Nephrolithiasis Risk (KD-Attributable): Chronic hypercalciuria (urinary Ca/Cr ratio up to 2.75) is a known metabolic consequence of KD-induced systemic acid load, which promotes bone resorption and renal calcium excretion [13,16]. Prophylactic administration of oral potassium citrate (Litocid/Citrolit) alkalinized the urine and successfully prevented stone formation over 10 years [16].

3. Osteopenia (KD-Attributable + Multifactorial): DXA-proven bone loss (Z-score -2.7) resulted from long-term ketosis and non-ambulatory status (GMFCS IV–V) [14]. Vitamin D3 and calcium supplementation were continued thereafter.

4. Transient Dyslipidemia (KD-Attributable): Serum total cholesterol and LDL elevations documented in 2020–2023 improved after dietary adjustments by 07/2026, consistent with the reversibility of KD-induced lipid changes reported in the literature [13,14].

4.5. Perioperative Safety of Ketogenic Diet

A particularly instructive event occurred in April 2018, when the patient required emergency craniotomy for a traumatic subdural hematoma. Perioperative management of patients on KD requires particular vigilance regarding inadvertent intravenous dextrose administration and loss of ketosis [6]. In our case, close coordination between pediatric neurosurgeons, anesthesiologists, and neurologists allowed continuous enteral KD administration throughout the perioperative window. The patient maintained therapeutic ketosis, experienced an uncomplicated surgical recovery, and suffered no postoperative seizure recurrence. This uncomplicated course is consistent with the favorable safety profile of dietary therapy reported in young children [17].

4.6. Enteral Compliance Without Gastrostomy

While gastrostomy tube (PEG) placement is routinely recommended for severely impaired children on long-term KD to ensure consistent ratio delivery [6], our patient's caregivers successfully maintained total oral feeding for >10 years using specialized texture-modified ketogenic recipes (e.g., ketogenic jellies and oil emulsions). Decade-long oral KD compliance is therefore achievable even in profound neurodevelopmental disability when family commitment and dietetic support are sustained [18].

4.7. Limitations

Several limitations inherent to single-case retrospective observations must be acknowledged:

1. Lack of Functional Electrophysiological Data: The specific nucleotide change (c. position) and functional gain- vs. loss-of-function status of the *SCN2A* exon 17 variant were not available in the hospital archival records, precluding direct biophysical channel modeling.

2. Qualitative Seizure Reporting: Seizure frequency was tracked via retrospective clinical discharge summaries rather than standardized daily parental diary logs.

3. Unstandardized Neurodevelopmental Scales: Formal psychometric testing and validated quality-of-life (QoL) inventories were not performed due to profound baseline intellectual disability.

4. Uncertainty Regarding Recent CBD Status: While CBD/THC co-therapy was documented from 2017 (5 drops/day) through 2023 (0.9 mL/day of 15% CBD oil), its exact dosage during the 2025–2026 hospitalizations were not detailed in the discharge summaries.

5. Inconsistent Archival Recordings: Gestational age at birth was recorded inconsistently (33–35 weeks) across hospital records; 34 weeks was adopted for this report. Likewise, some biochemical values from the early KD period were not retrievable from the available archival summaries.

The case was presented in accordance with the CARE reporting guidelines [19].

5. Conclusions

1. Continuous long-term Ketogenic Diet therapy (>10 years) is feasible, effective, and safe as a primary non-pharmacological treatment in severe *SCN2A*-related drug-resistant epileptic encephalopathy.

2. KD enabled complete withdrawal of conventional ASMs for nearly a decade, achieving sustained >50% seizure reduction and avoiding chronic ASM polypharmacy neurotoxicity.

3. Enteral KD can be safely maintained through major perioperative neurosurgical procedures without loss of ketosis or clinical destabilization.

4. Long-term safety requires proactive management of KD-attributable complications, specifically urine alkalinization for hypercalciuria, under a dedicated multidisciplinary pediatric team.

Declarations

- Ethics approval and consent to participate: Not applicable for a single anonymized case report; written informed consent for publication obtained from the parents.
- Consent for publication: Obtained from the patient's parents as above.
- Availability of data and materials: The data analyzed are contained within the patient's anonymized medical record. Further details are available from the corresponding author upon reasonable request, subject to privacy constraints.
- Competing interests: The authors declare that they have no competing interests.

Funding: No external funding was received for this work.

REFERENCES

1. Wolff, M., Johannesen, K. M., Hedrich, U. B. S., Masnada, S., Rubboli, G., Gardella, E., Lesca, G., Ville, D., Milh, M., Villard, L., Afenjar, A., Chantot-Bastaraud, S., Mignot, C., Lardennois, C., Nava, C., Schwarz, N., Gérard, M., Perrin, L., Doummar, D., … Møller, R. S. (2017). Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. *Brain, 140*(5), 1316–1336. https://doi.org/10.1093/brain/awx054
2. Sanders, S. J., Campbell, A. J., Cottrell, J. R., Møller, R. S., Wagner, F. F., Auldridge, A. L., Bernier, R. A., Catterall, W. A., Chung, W. K., Empfield, J. R., George, A. L., Hipp, J. F., Khwaja, O., Kiskinis, E., Lal, D., Malhotra, D., Millichap, J. J., Otis, T. S., Petrou, S., … Bender, K. J. (2018). Progress in understanding and treating SCN2A-mediated disorders. *Trends in Neurosciences, 41*(7), 442–456. https://doi.org/10.1016/j.tins.2018.03.011
3. Reynolds, C., King, M. D., & Gorman, K. M. (2020). The phenotypic spectrum of SCN2A-related epilepsy. *European Journal of Paediatric Neurology, 24*, 117–122. https://doi.org/10.1016/j.ejpn.2019.12.016
4. Howell, K. B., McMahon, J. M., Carvill, G. L., Tambunan, D., Mackay, M. T., Rodriguez-Casero, V., Webster, R., Clark, D., Freeman, J. L., Calvert, S., Olson, H. E., Mandelstam, S., Poduri, A., Mefford, H. C., Harvey, A. S., & Scheffer, I. E. (2015). SCN2A encephalopathy: A major cause of epilepsy of infancy with migrating focal seizures. *Neurology, 85*(11), 958–966. https://doi.org/10.1212/WNL.0000000000001926
5. Zuberi, S. M., Wirrell, E., Yozawitz, E., Wilmshurst, J. M., Specchio, N., Riney, K., Pressler, R., Auvin, S., Samia, P., Hirsch, E., Galicchio, S., Triki, C., Snead, O. C., Wiebe, S., Cross, J. H., Tinuper, P., Scheffer, I. E., Perucca, E., Moshé, S. L., & Nabbout, R. (2022). ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions. *Epilepsia, 63*(6), 1349–1397. https://doi.org/10.1111/epi.17239
6. Kossoff, E. H., Zupec-Kania, B. A., Auvin, S., Ballaban-Gil, K. R., Bergqvist, A. G. C., Blackford, R., Buchhalter, J. R., Caraballo, R. H., Cross, J. H., Dahlin, M. G., Donner, E. J., Guzel, O., Jehle, R. S., Klepper, J., Kang, H.-C., Lambrechts, D. A., Liu, Y. M. C., Nathan, J. K., Nordli, D. R., … Wirrell, E. C. (2018). Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open, 3*(2), 175–192. https://doi.org/10.1002/epi4.12225
7. Martin-McGill, K. J., Bresnahan, R., Levy, R. G., & Cooper, P. N. (2020). Ketogenic diets for drug-resistant epilepsy. *Cochrane Database of Systematic Reviews, 2020*(6), Article CD001903. https://doi.org/10.1002/14651858.CD001903.pub5
8. Neal, E. G., Chaffe, H., Schwartz, R. H., Lawson, M. S., Edwards, N., Fitzsimmons, G., Whitney, A., & Cross, J. H. (2008). The ketogenic diet for the treatment of childhood epilepsy: A randomised controlled trial. *The Lancet Neurology, 7*(6), 500–506. https://doi.org/10.1016/S1474-4422(08)70092-9
9. Kossoff, E. H., & Rho, J. M. (2009). Ketogenic diets: Evidence for short- and long-term efficacy. *Neurotherapeutics, 6*(2), 406–414. https://doi.org/10.1016/j.nurt.2009.01.005
10. Laux, L., & Blackford, R. (2013). The ketogenic diet in Dravet syndrome. *Journal of Child Neurology, 28*(8), 1041–1044. https://doi.org/10.1177/0883073813487599
11. Devinsky, O., Cross, J. H., Laux, L., Marsh, E., Miller, I., Nabbout, R., Scheffer, I. E., Thiele, E. A., & Wright, S. (2017). Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *New England Journal of Medicine, 376*(21), 2011–2020. https://doi.org/10.1056/NEJMoa1611618
12. Lattanzi, S., Trinka, E., Striano, P., Zaccara, G., Del Giovane, C., Nardone, R., Silvestrini, M., & Brigo, F. (2020). Cannabidiol efficacy and clobazam status: A systematic review and meta-analysis. *Epilepsia, 61*(6), 1090–1098. https://doi.org/10.1111/epi.16546
13. Kang, H. C., Chung, D. E., Kim, D. W., & Kim, H. D. (2004). Early- and late-onset complications of the ketogenic diet for intractable epilepsy. *Epilepsia, 45*(9), 1116–1123. https://doi.org/10.1111/j.0013-9580.2004.10004.x
14. Groesbeck, D. K., Bluml, R. M., & Kossoff, E. H. (2006). Long-term use of the ketogenic diet in the treatment of epilepsy. *Developmental Medicine & Child Neurology, 48*(12), 978–981. https://doi.org/10.1111/j.1469-8749.2006.tb01269.x
15. Best, T. H., Franz, D. N., Gilbert, D. L., Nelson, D. P., & Epstein, M. R. (2000). Cardiac complications in pediatric patients on the ketogenic diet. *Neurology, 54*(12), 2328–2330. https://doi.org/10.1212/WNL.54.12.2328
16. Sampath, A., Kossoff, E. H., Furth, S. L., Pyzik, P. L., & Vining, E. P. G. (2007). Kidney stones and the ketogenic diet: Risk factors and prevention. *Journal of Child Neurology, 22*(4), 375–378. https://doi.org/10.1177/0883073807301926
17. Dressler, A., Trimmel-Schwahofer, P., Reithofer, E., Gröppel, G., Mühlebner, A., Samueli, S., Grabner, V., Abraham, K., Benninger, F., & Feucht, M. (2015). The ketogenic diet in infants—Advantages of early use. *Epilepsy Research, 116*, 53–58. https://doi.org/10.1016/j.eplepsyres.2015.06.015
18. Wibisono, C., Rowe, N., Beavis, E., Kepreotes, H., Mackie, F. E., Lawson, J. A., & Cardamone, M. (2015). Ten-year single-center experience of the ketogenic diet: Factors influencing efficacy, tolerability, and compliance. *The Journal of Pediatrics, 166*(4), 1030–1036.e1. https://doi.org/10.1016/j.jpeds.2014.12.018
19. Gagnier, J. J., Kienle, G., Altman, D. G., Moher, D., Sox, H., & Riley, D. (2013). The CARE guidelines: Consensus-based clinical case reporting guideline development. *Journal of Medical Case Reports, 7*, Article 223. https://doi.org/10.1186/1752-1947-7-223

SUPPLEMENTARY MATERIAL

Supplementary Table S1. Chronological Paraclinical and Diagnostic Investigations

Date	Modality / Investigation	Key Clinical Findings & Parameters
07/2013	Transfontanellar USG	Non-dilated ventricular system; lateral ventricle width 19 mm (skull width 83 mm). Symmetric choroid plexuses. Normal extra-axial spaces.
07/2013	Abdominal USG	Liver length 74 mm without focal lesions. Acalculous gallbladder. Non-dilated bile ducts. Spleen 49 mm. Right kidney 52 mm, Left kidney 54 mm.
07/2013	Chest X-ray	Slightly increased bronchovascular markings, no infiltrates. Normal cardiac silhouettes. Prominent anterior mediastinum (thymus).
12/2013	Echocardiogram	Prior to ACTH-induced hypertrophic left ventricular cardiomyopathy. Tapering of antihypertensive therapy initiated.
04/2014	Echocardiogram	Normal systemic and pulmonary venous connections. IVSd 0.47 cm, LVD 2.51 cm, LVPWd 0.43 cm, FS 36.7%, EF 68.7%. False chordae in LV. No residual hypertrophy.
04/2014	Standard 12-lead EKG	Sinus rhythm 125 bpm. Normogram. PQ 0.10s, QRS 0.06s, QT 0.28s, QTc 0.40s. R wave in V4 25 mm.
04/2015	24-hour Holter EKG	Mean heart rate 117 bpm (61–174 bpm). No complex ventricular arrhythmias. No pauses exceeding 1.2 s. QTc 0.36–0.45s.
03/2016	Voiding Cystourethrography	Smooth bladder outline, complete empty post-micturition. No vesicoureteral reflux (VUR) was detected. Normal urethra.
10/2016	Barium Upper GI Series	Normal contrast transit through esophagus and stomach. No structural stenosis, no extrinsic compression, no gastroesophageal reflux.
04/2018	Cranial CT (Post-trauma)	Emergency post-traumatic subdural hematoma (57 × 19 × 65 mm) left temporoparietal area with mild cerebral edema and left parietal bone fracture, without midline shift. Emergency craniotomy performed; KD sustained perioperatively.
09/2018	22-hour Holter EEG	Abnormal background (theta-alpha 4–7 Hz). Paroxysmal series of high-voltage sharp waves/spikes (200–300 μV) and slow delta-theta waves (3–5 Hz, 150–220 μV) central-parietal bilaterally (left predominance).
07/2019	24-hour Holter EEG	Persistent bilateral temporal spike-wave complexes (3–7 Hz, 200–300 μV) during NREM sleep and drowsiness.
07/2019	Lumbar Spine DXA	BMD Z-score: -2.7 (significant osteopenia of the lumbar spine L1–L4).
01/2023	Routine Scalp EEG	Bilateral temporal-parietal spike-wave complexes; mild electrographic deterioration compared to 2019 Holter EEG.
05/2026	Echocardiogram	IVSd 6.5 mm, LVPWd 5.6 mm, FS 34%, EF 63%, MAPSE 16.8 mm, TAPSE 18.3 mm. Ascending aorta Z-score +1.4. LV false chordae. Normal valvular function.

Supplementary Table S2. Complication Profile and Causal Attribution

Complication / Adverse Event	Onset Date	Causal Attribution to KD	Clinical Management & Outcome
Hypertrophic Cardiomyopathy	2013–2014	Unrelated to KD (Secondary to ACTH/Synacten)	Discontinuation of ACTH, multi-drug antihypertensive therapy (captopril, metoprolol, spironolactone, amlodipine). Complete echocardiographic resolution prior to KD initiation.
Hypercalciuria & Crystalluria	2016 (Persistent)	KD-Attributable (Ketosis-induced urinary acidification)	Oral alkalinization with Potassium Citrate (Litocid/Citrolit) and low-dose Furazydine (Furagin). No nephrolithiasis on serial USG.
Lumbar Osteopenia (Z-score -2.7)	07/2019	KD-Attributable (+ non-ambulatory status GMFCS IV–V)	Oral vitamin D3 and calcium supplementation.
Transient Mixed Dyslipidemia	2020–2023	KD-Attributable (High saturated fat intake on classic KD)	Dietary ratio adjustments (1.75:1 → MAD → 2:1). Lipid panel normalized by 07/2026 (Total Cholesterol 162 mg/dL, LDL 110.5 mg/dL).
Traumatic Subdural Hematoma	04/2018	Unrelated to KD (Accidental head injury)	Emergency, craniotomy and surgical evacuation. Enteral KD sustained perioperatively without metabolic or surgical complications.
Hypothyroidism	2013	Unrelated to KD (Pre-existing congenital/infantile)	Managed with Levothyroxine (Euthyrox 12.5 µg/day) with euthyroid status throughout follow-up.
Metabolic Acidosis Episode	09/2018	KD-Attributable (Exacerbated during intercurrent illness)	Supportive management with hydration; acidosis resolved before discharge.