The relation of etiology based on the 2017 ILAE classification to the effectiveness of the ketogenic diet in drug-resistant epilepsy in childhood

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Abstract

Objective: To investigate the effectiveness and safety of the ketogenic diet (KD) in drug-resistant epilepsy in childhood in relation to the new 2017 International League Against Epilepsy (ILAE) classification of etiology.

Methods: A consecutive cohort of patients treated with the KD were categorized according to the ILAE classification into known (structural, genetic, metabolic, infectious, and immune-mediated) and unknown etiology. Primary outcome was the frequency of patients achieving seizure freedom with the KD at 3 months, secondary outcomes were seizure reduction >50% at 3 months, and both seizure freedom and seizure reduction >50% at 6, 12 months, and at last follow-up (LFU), and adverse effects. Outcomes were compared between etiology groups.

Results: Etiology was known in 70% (129/183). Outcomes did not differ at 3 months (known vs unknown: seizure freedom 28% vs 33%, seizure reduction 62 vs 67%), but seizure freedom was significantly less frequent in known etiology at 6 months (26% vs 43%) and beyond (22% vs 37%). Logistic regression identified duration of epilepsy, number of previous antiseizure medications (ASMs), and age-appropriate psychomotor development as positive determinants of outcome. Among individual etiology groups, the effectiveness of KD was relatively best for genetic (33% at LFU) and poorest for metabolic etiology (8% at LFU). The small number of patients with infectious and immune-mediated etiology requires larger numbers in each etiology group to corroborate our results. No differences in type and frequency of adverse effects (in 71%) between etiology groups were observed, requiring medical intervention in 21%.

Significance: The KD was most effective in genetic and unknown etiology, many unknowns probably represent yet unidentified genetic causes. We recommend consequent diagnostic and genetic work-up to identify etiologies that respond...
1 | INTRODUCTION

The ketogenic diet (KD) is a high fat, low carbohydrate diet that has been used since the 1920s in the treatment of drug-resistant epilepsies of childhood. Its use in drug-resistant epilepsy in childhood has increased steadily during the last years, supported by randomized-controlled studies supporting its effectiveness and safety. An updated Cochrane systematic review of 2020 included 13 studies with 932 participants. The authors concluded that the KD could demonstrate effectiveness in childhood, but that evidence for the use in adulthood remains uncertain. Drug resistance in epilepsy is defined as the failure of at least two appropriately used antiseizure medications (ASMs), given in adequate dosage either alone or in combination, to achieve seizure freedom. Despite the availability of more than 20 new ASMs in the last decades, drug resistance is still challenging. In addition, recent reports have shown that after the fourth drug, only 14% of patients will become seizure-free. The primary aim of ASMs is to suppress seizures; these agents do not sufficiently modify the disease process or prevent the progression of epilepsy. Epileptogenesis is defined as the capability of tissue to develop spontaneous seizures resulting in the development of an epileptic disorder and/or the progression of the epileptic disease. Consequently, new therapeutic strategies need not only suppress seizures but also to prevent or reverse epileptogenesis and/or correct genetic deficiencies, which means they should exert antiepileptogenic effects. In some forms of genetic epilepsies, individualized treatments that directly address the function of the genetic defect, such as the KD in solute carrier 2A1 (SLC2A1) mutations responsible for Glucose transporter type 1 deficiency syndrome (GLUT1 deficiency), have been associated with seizure reduction and improved neurodevelopment. In addition, after a first unprovoked seizure, a known etiology together with epileptiform patterns on electroencephalography (EEG) has been associated with an almost threefold increase in the recurrence risk, compared to epilepsy of unknown etiology without changes in EEG. This suggests that epileptogenesis has already started in certain known epilepsies when epileptiform patterns are already present.

KEYWORDS

drug-resistant epilepsy, epilepsy syndromes, etiology, ILAE classification, ketogenic diet, seizure freedom

Key points

- No differences in effectiveness of the ketogenic diet (KD) between known and unknown etiology at 3 months after KD-start
- Seizure freedom less frequent in known vs. unknown etiology at 6 months and beyond
- Duration of epilepsy, number of antiseizure medications and age-appropriate development before KD are positive determinants of outcome
- Effectiveness relatively best for genetic and unknown etiology
- Offer KD early in genetic and unknown etiology before deterioration of psychomotor development

Therefore, prompt diagnosis and specific treatment on the basis of the underlying etiology and electroclinical syndrome are crucial for timely seizure control and, hence, for developmental outcome, with seizure freedom being the critical outcome parameter. For these reasons, all known etiologies need to be identified early to start the most appropriate specific treatments including the KD. This is particularly important for the KD as it exerts antiepileptogenic and disease-modifying effects. Early start of the KD has previously been shown to be associated with positive seizure outcome. Consequentially, an early use of the KD with the diet’s ability to modify the epileptic encephalopathy process might hold back the limit deterioration of cognitive function, which is the downside of some antiseizure medications. Therefore, it is important to identify etiologies that respond best to the KD, in order to offer the KD as soon as possible to specific target populations but to spare patients from this restrictive diet regimen who are less likely to respond. The new guidelines for the management of the KD of 2018 clarified indications for its use, with a special emphasis on etiologies and electroclinical syndromes. In 2017, the International League against epilepsy (ILAE) introduced a new classification for known etiology groups (structural, genetic, metabolic, infectious, and immune-mediated).
However, previous studies reporting on the effectiveness of the KD have mostly not differentiated between etiologies according to the ILAE classification criteria, and seizure freedom as outcome parameter, an established outcome after epilepsy surgery, has not been used widely for the KD. The aims of the present study were to assess the effectiveness and safety of the KD in drug-resistant epilepsy in relation to the new ILAE classification of epilepsy etiology by

1. Comparing patients with known v. those with unknown etiology.
2. Comparing between ILAE etiology groups (structural, genetic, metabolic, infectious, and immune mediated) and unknown etiology,
3. Using seizure freedom as a primary outcome measure, and
4. Accounting for clinical co-variables also affecting the outcome.

2 | METHODS

2.1 | Study design

This was a cohort study of consecutive patients with epilepsy treated with the KD at the Medical University of Vienna Department of Pediatrics and Adolescent Medicine from March 1999 to January 2019. We maintain a database of prospectively and longitudinally collected data on patients’ demographics and medical history, laboratory results, seizure control, and developmental outcomes, as well as on the tolerability of the KD.

For the purpose of the present study, all demographic and diagnostic data and data on the effectiveness and safety of the KD were extracted from this database. The study was approved by the ethics committee of the Medical University of Vienna (EK-Nr. 1590/2019).

2.2 | Study population

Study inclusion criteria were complete clinical data (including detailed seizure diaries) and an observation period of at least 3 months after initiation of the KD. For this study, all patients who received the diet for 3 months or more were included. Patients were categorized according to the 2017 ILAE classification of epilepsy into the following etiology groups: known (structural, genetic, metabolic, infectious, and immune etiologies) and unknown causes. The concept of a structural or metabolic etiology is that the cerebral lesion or metabolic condition increases the risk of associated epilepsy. As proposed by the ILAE 2017, when a genetic cause was found (eg, tuberous sclerosis or GLUT1 deficiency), these conditions were grouped into the structural or metabolic group. Thus we assigned patients into the genetic group in cases where a conclusive genetic diagnosis supported the concept of genetic epilepsy directly caused by a known or by a probably damaging mutation. We display mutations (Table S1) that have already been reported or are predicted to be probably damaging by in silico prediction tools.

2.3 | Introduction of the KD and follow-up visits

At the baseline visit prior to the KD start, the assessment included a complete medical workup, as indicated by standard of care and current guidelines for epilepsy. Demographic and diagnostic data were collected (gender, etiology, age at epilepsy onset, duration of epilepsy before KD start, number of ASMs before and at KD start, epilepsy syndrome, seizure frequency).

The KD was introduced without fasting and fluid restriction at a 1:1 fat/nonfat ratio and individually increased up to 3:1 (modified when beta-hydroxybutyrate levels were >5 mmol/L) including an age-appropriate intake of protein. Parents documented adverse effects in an adverse effect questionnaire. The questionnaire was assessed at each visit.

Follow-up visits were scheduled at 1, 3, 6, and 12 months, and then every 6 months. At each visit, pediatric, nutritional, and neurological examinations, as well as video-EEG were performed. Treatment response was calculated by parental seizure count documented in a seizure diary. The number of seizures was assessed and compared to baseline visit. Children who showed a lower than 50% seizure reduction after 3 months were regarded as nonresponders and discontinued the diet but were further followed in this cohort.

2.4 | Study outcomes

Primary study outcome was the presence of seizure freedom (100% seizure reduction) at 3 months after the start of the KD. Secondary outcome parameters were frequencies of

1. Seizure reduction (of >50%) at 3, 6, 12 months and at last follow-up visit (LFU; >12 months);
2. Seizure freedom at 6 and 12 months and at LFU;
3. Type and frequency of adverse effects in response to the KD.
2.5 | Data analysis

We used the IBM Statistical Package for Social Science (SPSS Statistics Version 26) for analysis. Descriptive statistics included medians, minimums, maximums, numbers, and percent, where appropriate. For comparisons between groups, we calculated differences in medians or odds ratios with 95% confidence intervals, and parametric or nonparametric tests were used as appropriate (k-test of the median, Pearson’s chi-square or Fisher’s exact test). Odds ratios for comparing epilepsy outcomes between known and unknown etiology groups were adjusted for relevant prognostic clinical cofactors by logistic regression, using stepwise forward inclusion of covariables and reporting the results of the best predictive models. ILAE etiology groups were compared with unknown etiology without adjusting for covariables because of small patient numbers per group. Because this was an exploratory analysis, the significance level was kept at $p \leq .05$, not accounting for multiple comparisons. For the comparison of individual etiologies, we display only descriptive statistics because of small patient numbers.

3 | RESULTS

3.1 | Study population

Two hundred one patients received the KD during the study period from March 1999 until January 2019. Dropouts due to noncompliance with the KD occurred in 17 children (8.4%) during the first weeks of evaluation. One child received the KD because of a complex I deficiency without seizures. These eighteen patients were therefore not included in the analysis. The final cohort consisted of 183 patients, of whom 46% (85/183) were female. Four patients were adults: two with GLUT1 deficiency, one with epilepsy after limbic encephalitis, and one with generalized tonic-clonic seizure (GTCS).

3.1.1 | Patient characteristics overall

Patients’ age at epilepsy onset was median 4.8 months (minimum 0 months, maximum 16.2 years) and the age at KD start was median 14.4 months (minimum 0 months, maximum 42.3 years). The duration of epilepsy before the KD start was median 7.2 months (minimum 0 months, maximum 39.6 years). The number of ASMs used before KD initiation was median 3 (0, 13). At KD start, 90.7% (166/183) of patients received concomitant ASMs (median 2; 0, 5). Seventeen patients had received the KD as first-line therapy for epilepsy syndrome and etiology according to KD consensus guidelines.3 Psychomotor development was age appropriate in 17% (31/183). Fat/nonfat ratio of the KD was median 3:1 (2:1-4:1); 14 patients received a modified Atkins diet (MAD). The duration of the KD was median 9.6 months (2.4 months; 12.6 years); the duration of follow-up was median 3.9 years (2.5 months; 15.3 years).

3.1.2 | Etiology of epilepsy by ILAE classification

Etiology of epilepsy was known in 70% (129/183) of patients and unknown in 30% (54/183).

According to the 2017 ILAE classification of etiology groups, structural causes were present in 52% (67/129), genetic causes in 33% (43/129), metabolic causes in 10% (13/129), infectious causes in 4% (5/129), and immune-mediated cause in 1% (1/129). The relative distribution of etiology groups is displayed in Figure 1. Individual etiologies are listed in Table 5, and individual genetic mutations are listed in Table S1.

3.1.3 | Patient characteristics at baseline by ILAE etiology groups

Table 1 shows patient characteristics at baseline by known vs unknown etiology. Patients with unknown etiology more frequently had age-appropriate psychomotor development at the KD start. There were no significant differences in other variables.

Table 2 shows patient characteristics at baseline by etiology groups (structural, genetic, metabolic, and infectious) vs. unknown etiology. As immune-mediated cause was observed in only one patient, this group is not displayed in Table 2. Patients with structural etiology were younger at epilepsy onset, and patients with genetic etiology had used a higher number of ASMs prior to the KD and less frequently showed age-appropriate psychomotor development than patients with unknown etiology.

3.2 | Study outcomes

3.2.1 | Overall effectiveness of the KD

The primary outcome, seizure freedom at 3 months, was achieved in overall 30% (54/183) of patients. Seizure reduction of $>50\%$ was achieved in 63% (116/183) of patients at 3 months; 55% (101/183) at 6 months, and 46% (84/183) at 12 months and at LFU. Seizure freedom was achieved in 31% (57/183) at 6 months, and 26% (48/183) both at 12 months and at LFU. ASMs could be tapered...
during the KD in 31% (57/183) of patients by LFU; in 5% (9/183) of patients, ASMs could be tapered due to other interventions such as other ASM treatment and/or epilepsy surgery. At LFU, 11% (21/183) of patients were still on the KD, including the pediatric patient with GLUT1 deficiency who was seizure-free.

### 3.2.2 Effectiveness of the KD by known vs unknown etiology

Table 3 shows study outcomes comparing known vs unknown etiology. At 3 months, the frequency of seizure freedom as well as seizure reduction >50% did not differ between patients with known etiology compared to unknown etiology.

However, seizure freedom at 6 and 12 months, and at LFU was significantly less frequent in patients with known etiology than in patients with unknown etiology. When adjusting for relevant covariables (duration of epilepsy, number of ASMs before the KD start, or age-appropriate psychomotor development), this difference was significant only for seizure freedom at 6 months, but trends remained at 12 months and at LFU. Similar trends were also seen for seizure reduction at 6 and 12 months.

Our logistic regression models identified duration of epilepsy, number of ASMs before the KD start, and age-appropriate psychomotor development as independent prognostic factors positively associated with the effectiveness of the KD, that partially explained some of the differences in outcome between known and unknown etiologies.
Figure 2A,B shows the percentages of seizure freedom and of seizure reduction >50% by known vs unknown etiology over time. At 3 months, the two groups did not differ, the curves separate by 6 months. In patients with known etiology, seizure freedom and seizure reduction >50% was most frequent at 3 months and then gradually declined at 6 and 12 months. In contrast, in patients with unknown etiology, seizure freedom was least frequent at 3 months, but increased at 6 months and then stabilized both at 12 months and at LFU. Seizure reduction >50% also declined after 3 months.

### 3.2.3 Effectiveness of the KD by ILAE etiology groups

Table 4 shows the study outcomes in the different ILAE etiology groups vs unknown etiology. The following significant differences to patients with unknown etiology were found: Patients with structural etiology showed a lower frequency of seizure freedom at 12 months; those with metabolic etiology showed lower frequencies of seizure reduction at 3, 6, and 12 months and at LFU, as well as a lower frequency of seizure freedom at last follow-up.

| Etiology known (n = 129) | Etiology unknown (n = 54) | Unadjusted OR (CI 95%) | p-Value | Adjusted OR* (CI 95%) | Adjusted p-Value* |
|-------------------------|-------------------------|------------------------|---------|-----------------------|------------------|
| Seizure freedom at 3 months | 36 (28%) | 18 (33%) | 0.77 (0.4–1.54) | .481 | 1.03 (0.50–2.14) | .930 |
| Seizure reduction >50% at 3 months | 80 (62%) | 36 (67%) | 0.82 (0.42–1.59) | .552 | 1.04 (0.51–2.10) | .920 |
| Seizure reduction >50% at 6 months | 67 (52%) | 34 (63%) | 0.64 (0.33–1.22) | .173 | 0.71 (0.36–1.38) | .309 |
| Seizure reduction >50% at 12 months | 55 (43%) | 29 (54%) | 0.64 (0.34–1.21) | .172 | 0.67 (0.35–1.28) | .223 |
| Seizure freedom at 6 months | 34 (26%) | 23 (43%) | 0.48 (0.25–0.94) | .032 | 0.50 (0.25–1.0) | .049 |
| Seizure freedom at 12 months | 28 (22%) | 20 (37%) | 0.47 (0.24–0.94) | .032 | 0.62 (0.29–1.32) | .212 |
| Seizure freedom at last follow-up | 28 (22%) | 20 (37%) | 0.47 (0.24–0.94) | .032 | 0.62 (0.29–1.32) | .212 |
| Adverse effects of the KD | 92 (71%) | 38 (70%) | 1.05 (0.52–2.10) | .898 |
as of seizure freedom at 12 months and at LFU; and patients with infectious etiology showed a lower frequency of seizure reduction at 12 months. Figure S1 also displays percentages of seizure freedom, seizure reduction >50%, and of nonresponse at LFU in the different ILAE etiology groups. The highest frequencies of seizure freedom were observed in unknown followed by genetic etiologies. In addition, the frequencies of nonresponse were similar in unknown and genetic etiologies. Nonresponse was observed most frequently in metabolic etiologies.

3.2.4 | Effectiveness of the KD by individual etiologies

Table 5 shows the effectiveness of the KD (seizure reduction >50% at 12 months, seizure freedom at LFU) by individual etiologies. Seizure freedom at LFU was seen only in single patients except for Down syndrome (75%).

In the subgroup of focal cortical malformations, seizure freedom was observed in 15% ($n = 5$), and seizure reduction >50% in 33% ($n = 13$). Ten of these 13 patients had a seizure reduction of >50%, namely of 90% to 99%. The majority of the patients had malformations of postmigrational development (80% of seizure-free patients; 54% of patients with seizure reduction >50%).

3.2.5 | Effectiveness of the KD by epilepsy syndromes

Table S2 shows the effectiveness of the KD (seizure reduction >50% at 12 months, seizure freedom at LFU) by epilepsy syndromes.
3.2.6 | Safety of the KD

Adverse effects to the KD overall were observed in 71% (130/183) of patients. None of the adverse effects necessitated interruption of the diet and most were resolved by dietary modifications. Adverse effects needing medical intervention were observed in 21% (39/183), requiring infusion in 9% (16/183), antibiotics in 9% (17/183), and tube feeding in 3% (6/183).

Frequencies and types of adverse effects did not differ between known or unknown etiology (Table 3) and not between etiology groups (Table 4).

4 | DISCUSSION

In this consecutive cohort of patients receiving the KD, we evaluated the effectiveness of the KD in relation to epilepsy etiology based on the 2017 ILAE classification. Patients with known etiology showed lower frequencies of seizure freedom that were almost half when compared to those with unknown etiology at 6 and 12 months and at LFU (>12 months). For seizure reduction >50% at 6 and 12 months, we observed similar trends. Of interest, at 3 months after introduction of KD, these differences in outcome were not yet observed. Accounting for relevant covariables in logistic regression models, we identified a shorter duration of epilepsy, a lower number of ASMs prior to KD, and better psychomotor development at the KD start as relevant prognostic factors for the effectiveness of the KD, which partially explained some of the differences between known and unknown etiology groups.

For specific ILAE etiology groups, all groups had lower frequencies of seizure freedom beyond 6 months compared to unknown etiology, which were relatively best for genetic etiology and poorest for metabolic etiology. For metabolic etiology, this was also reflected in the frequencies of seizure reduction.

Our study is significant for two reasons. First, the results provide clinicians a better understanding of the effectiveness of the KD and the prognosis in different groups of known and unknown etiologies. One goal of epilepsy research and therapy is to develop toward precision medicine, meaning that individuals with genetic and other epilepsies should be treated with therapies targeted specifically to their individual etiology. Second, our findings provide further evidence that the KD, used in specific target indications, should be started as early as possible to be the most effective. This includes an early etiologic diagnosis including novel genetic techniques and the KD as early treatment in specific epilepsy syndromes such as West syndrome or GLUT1 deficiency. Furthermore, as recommended in the literature, considering the poor success of conventional ASMs and early drug resistance in epileptic encephalopathies, the early use of corticosteroids and the KD is also recommended in specific conditions.

In the past, research has focused on assessing the effectiveness of the KD with mostly retrospective studies and some randomized controlled trials. The KD management guidelines recommend the prospective study of which etiologies respond best to the KD in drug-resistant epilepsy when ASMs have failed or are not likely to be successful. Our prospective study assesses the effectiveness of the KD by etiology based on the new (2017) ILAE classification. This classification has been developed to standardize care and to identify target populations for individualized treatment including the KD.
In drug-resistant epilepsy of various etiology, seizure reduction and seizure freedom in response to ASMs has been reported to be lower than the response to the KD, \(^6,10\) which we see as an expression of established drug resistance and ongoing epileptogenesis when ASMs are not successful and as a sign of the antiepileptogenic effects of the KD. A lack of response to adequately used ASMs is an expression of established drug resistance and evolving epileptogenesis, whereas patients may still respond to the KD because of its antiepileptogenic effects. For known etiologies, the effectiveness of the KD decreases after 3 months compared to unknown etiologies. This could be seen in analogy to the drug resistance of ASMs.

In our opinion, this pattern reflects the mechanism of drug resistance, when any new therapeutic scheme shows some benefit during the first 3–6 months with seizure frequency returning to baseline thereafter.\(^8\) In contrast, for unknown etiologies, the effectiveness of the KD further increased after 3 months. We hypothesize that these results indicate that the KD can apparently overcome the point of no return in epileptogenesis and modify disease progression, as discussed previously in the literature.\(^{19,20}\) We hypothesize that resistance to treatment during KD is not yet final.\(^{24,39,40}\) Moreover, ASMs could be tapered during the KD in the majority of our patients.

In our study, seizure freedom in structural etiology, specifically in cortical malformations, was comparable to reports in the literature,\(^{41}\) as well as seizure reduction of >50% and with the majority showing even a higher seizure reduction of >90%, most likely due to a majority of patients with postmigrational development.\(^{42}\)

### TABLE 5 Effectiveness of the KD by individual etiologies

| Etiology                                    | No. of patients | Seizure reduction >50% at 12 months | Seizure freedom at LFU |
|---------------------------------------------|-----------------|-------------------------------------|------------------------|
| **Total**                                   | 183             |                                    |                        |
| Structural etiologies                       | 67              | 28 (42%)                            | 13 (19%)               |
| Cortical malformations                      | 33              | 13 (39%)                            | 5 (15%)                |
| Vascular/ischemic                           | 23              | 10 (43%)                            | 4 (17%)                |
| Tuberous sclerosis                          | 4               | 3 (75%)                             | 0 (0%)                 |
| Incomplete opercularization                 | 3               | 1 (33%)                             | 1 (33%)                |
| Schimmelpenning-Feuerstein-Mims syndrome    | 1               | 1 (100%)                            | 1 (100%)               |
| White matter atrophy                        | 1               | 0 (0%)                              | 0 (0%)                 |
| Joubert syndrome                            | 1               | 0 (0%)                              | 0 (0%)                 |
| Pontocerebellar hypoplasia                  | 1               | 0 (0%)                              | 0 (0%)                 |
| **Genetic etiologies**                      | 43              | 24 (56%)                            | 13 (30%)               |
| Dravet syndrome                             | 14              | 9 (64%)                             | 1 (7%)                 |
| Down syndrome                               | 4               | 4 (100%)                            | 3 (75%)                |
| SCN2A                                       | 3               | 2 (67%)                             | 1 (33%)                |
| CDKL5                                       | 2               | 0 (0%)                              | 0 (0%)                 |
| Angelman syndrome (UBE3A)                   | 1               | 0 (0%)                              | 0 (0%)                 |
| GRIN2A                                      | 1               | 0 (0%)                              | 0 (0%)                 |
| **Other genetic causes**                    | 18              | 11 (61%)                            | 8 (44%)                |
| Metabolic etiologies                        | 13              | 2 (15%)                             | 1 (8%)                 |
| Mitochondriopathy                           | 5               | 1 (20%)                             | 0 (0%)                 |
| GLUT1 deficiency syndrome                   | 3               | 1 (33%)                             | 1 (33%)                |
| Non-ketotic hyperglycinemia                 | 2               | 0 (0%)                              | 0 (0%)                 |
| Neuronal cerebral lipofuscinosis            | 1               | 0 (0%)                              | 0 (0%)                 |
| Unverricht-Lundborg syndrome                | 1               | 0 (0%)                              | 0 (0%)                 |
| GABA-transaminase deficiency syndrome       | 1               | 0 (0%)                              | 0 (0%)                 |
| **Metabolic etiologies**                    | 13              | 2 (15%)                             | 1 (8%)                 |
| Mitochondriopathy                           | 5               | 1 (20%)                             | 0 (0%)                 |
| GLUT1 deficiency syndrome                   | 3               | 1 (33%)                             | 1 (33%)                |
| Non-ketotic hyperglycinemia                 | 2               | 0 (0%)                              | 0 (0%)                 |
| Neuronal cerebral lipofuscinosis            | 1               | 0 (0%)                              | 0 (0%)                 |
| Unverricht-Lundborg syndrome                | 1               | 0 (0%)                              | 0 (0%)                 |
| GABA-transaminase deficiency syndrome       | 1               | 0 (0%)                              | 0 (0%)                 |
| **Infectious etiologies**                   | 5               | 0 (0%)                              | 0 (0%)                 |
| Immune-mediated etiology                    | 1               | 1 (100%)                            | 1 (100%)               |

Abbreviations: Cyclin-dependent kinase-like 5 (CDKL5), Glucose transporter 1 (GLUT1), Glutamate receptor ionotropic NMDA 2A (GRIN2A), KD, ketogenic diet; LFU, last follow-up, Sodium voltage-gated channel alpha subunit 1 (SCN1A), Ubiquitin-protein ligase E3A (UBE3A).

Significance: \(^{*}\)See Figure 1 and Table S1 for other genetic causes.
In the vascular/ischemic subgroup, our results were also in line with previous studies on patients with structural abnormalities due to hypoxic-ischemic encephalopathy. In hypoxic-ischemic encephalopathy and post-stroke epilepsy, the KD is increasingly considered as an early treatment option because of its anti-inflammatory properties and reduction of excitotoxicity, oxidative stress, and apoptosis. This approach is supported by an animal model showing that the KD improved early motor behavior after cerebral ischemic stroke.

In metabolic epilepsies, only single patients showed seizure freedom as well as seizure reduction >50%; notably, only one patient with GLUT1 deficiency starting the KD in infancy. All other GLUT1 patients were diagnosed in adolescence or young adulthood through genetic testing, and showed improvement only of motor symptoms and dystonia, but not of seizures. Considering that the KD is the treatment of choice in GLUT1 deficiency, we conclude that early diagnosis in infancy is essential.

In our group of genetic epiletiologies, a high percentage of response to the KD was observed for Dravet syndrome, Down syndrome, SCN2A mutation, and other genetic causes. This effectiveness of the KD was somewhat higher than described previously, except for similar frequencies of response reported by Kim and coworkers for the genetic group overall, and by Ko and coworkers for some individual genetic entities. Ko and coworkers showed a high percentage of seizure reduction of >50% in identified genetic epilepsies, including Dravet syndrome, SCN2A, but not CDKL5 (comparable to our data). Our study was the largest among these studies, and we reported frequencies of seizure freedom for all identified individual genetic entities.

We speculate that the comparable effectiveness of the KD in unknown and genetic etiology suggests that many unknown etiologies likely represent yet-unidentified genetic causes. Thus such genetic etiologies should be identified to the extent possible and treated with the KD as appropriate.

Positive determinants of seizure outcome such as early KD treatment, young age at start, and age-appropriate development, although not observed by all previous studies, are in line with consensus guidelines. Accordingly, the KD should be started early, before psychomotor development has deteriorated, as this optimizes the antiepileptogenic, disease-modifying effects of the KD.

In our experience, the safety of the KD was good, with adverse effects needing medical intervention in only 21% of patients. Adverse effects did not differ between etiology groups, as all metabolic and clinical contraindications for the KD were always ruled out and initiation of the KD at our center includes a gradual and individualized diet regimen.

There are some limitations of our study to consider. First, the limited number of patients per known etiology groups allowed only descriptive comparisons between subgroups and limits the definition of new target populations for the KD on the basis of pathophysiology. In addition, numbers of patients with infectious and with immune-mediated etiology were small. Further studies with larger numbers of patients in each etiology group will be necessary to corroborate our results.

Second, our genetic data were collected as part of our clinical routine. This is a limitation, because genetic testing has undergone enormous changes over the last two decades: from sequencing of single genes when a striking clinical pattern occurred (eg, in Dravet syndrome) to panel diagnostics where several genes associated with childhood epilepsy are sequenced. Recently, next generation sequencing methods including whole-exome and whole-genome sequencing have become part of clinical practice. Therefore, patients with unknown etiology at the time of treatment, when re-studied now, might have a genetic cause identified. Similar frequencies of seizure reduction and of seizure freedom in our groups with genetic and unknown etiologies hint to many unknowns having genetic causes, which will be an important focus of our future research.

Third, we did not further subclassify etiology groups in terms of electroclinical syndromes. We have analyzed the effectiveness of the KD by epilepsy syndromes showing a significantly better response to the KD in some, such as West syndrome, Lennox-Gastaut syndrome, Dravet syndrome, and myoclonic atonic epilepsy. However, we have refrained from further subclassification of etiology groups into syndromes for reasons of sample size and to avoid overinterpretation of the data.

The strengths of our study are the prospective data collection and the large sample, resulting in large numbers of patients in the two main groups of known vs unknown etiology. Because we are the only quaternary national center with a pediatric epilepsy surgery program in Austria, our study sample comprises a concentration of patients with drug-resistant epilepsy.

In summary, our study shows the KD to be a feasible, effective, and safe treatment in drug-resistant epilepsy. The effectiveness of the KD was best in patients with genetic etiology and those with unknown etiology, many of the latter likely representing yet-unidentified genetic causes. We conclude that the KD should be offered earlier to infants diagnosed with genetic epilepsy, even before drug resistance has developed. Moreover, consequent diagnostic workup and genetic testing to identify etiologies that respond best to the KD are useful for targeted therapy from the start. Moreover, the KD has the highest effectiveness when started before any deterioration of psychomotor development.
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CONFLICT OF INTEREST
The other authors have no conflicts of interest to disclose.

INFORMED CONSENT
Written informed consent was obtained from all carers and/or participants.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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