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KCNT1-related epilepsy: An International Multicenter Cohort of 27 Pediatric Cases

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ABSTRACT

Objective: Through international collaboration, we evaluated the phenotypic aspects of a multiethnic cohort of KCNT1-related epilepsy and explored genotype-phenotype correlations associated with frequently encountered variants.

Methods: A cross-sectional analysis of children harboring pathogenic or likely pathogenic *KCNT1* variants was completed. Children with one of the two more common

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recurrent *KCNT1* variants were compared to the rest of the cohort for the presence of particular characteristics.

Results: Twenty-seven children (15 males, mean age 40.8 months) were included. Seizure onset ranged from one day to six months, and half (48.1%) exhibited developmental plateauing upon onset. Two-thirds had epilepsy of infancy with migrating focal seizures (EIMFS) and focal tonic seizures were common (48.1%). The most frequent recurrent *KCNT1* variants were c.2800G>A; p.Ala934Thr (n=5) and c.862G>A; p.Gly288Ser (n=4). *De novo* variants were found in 96% of tested parents (23/24). Sixty percent had abnormal MRI findings. Delayed myelination, thin corpus callosum, and brain atrophy were most common. One child had grey-white matter interface indistinctness, suggesting a malformation of cortical development. Several anti-epileptic drugs (mean 7.4/patient) were tried with no consistent response to any one agent. Eleven tried quinidine, 45% had marked (>50% seizure reduction); or some improvement (25-50% seizure reduction). Seven used cannabidiol, 71% experienced marked or some improvement. Fourteen tried diet therapies, 57% had marked or some improvement. When comparing the recurrent variants to the rest of the cohort, with respect to developmental trajectory, presence of EIMFS, >500 seizures/month, abnormal MRI and treatment response, there were no statistically significant differences. Four patients died (15%); none of SUDEP.

Significance: Our cohort reinforces common aspects of this highly pleiotropic entity. EIMFS manifesting with refractory tonic seizures was most common. Cannabidiol, diet therapy, and quinidine seem to offer better chances of seizure reduction, although evidence-based practice is still unavailable.

Key words: *KCNT1*, Epilepsy of infancy with migrating focal seizures, microcephaly, CBD, ketogenic diet, quinidine.

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INTRODUCTION

KCNT1 encodes a ligand-gated potassium channel, which is activated by intracellular sodium binding (also called SLACK, SLO2.2, KC4.1). KCNT1 has several functions, which include regulating neuronal firing rate, contributing to the slow hyperpolarization after repetitive firing, and it also has an important role in neuronal response to hypoxia.[1-3] Gain-of-function effects produce higher action potential firing frequency due to faster action potential repolarization and increased fast after-hyperpolarization.[4] KCNT1 channels are widely expressed in the central nervous system and are found in the olfactory bulb, brainstem, hippocampal and cortical embryonic neurons.[1,2,5]

Gain of function *KCNT1* pathogenic variants are known to cause pleiotropic effects and a number of epilepsy phenotypes have been described: (I) epilepsy of infancy with migrating focal seizures (EIMFS);[1,6] (II) a severe form of autosomal dominant sleep-related hypermotor epilepsy (ADSHE);[7] (III) Early onset epileptic encephalopathy (EOEE) (i.e. Ohtahara syndrome, West syndrome, and unclassified EOEE);[8] (IV) temporal lobe epilepsy with intellectual disability;[9] and (V) myoclonic-atonic epilepsy.[10] Although most patients harbouring *KCNT1* pathogenic variants have no causative underlying structural brain abnormalities, patients with ADSHE may rarely exhibit malformations of cortical development.[11]

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There has been inconsistent data with respect to clinical efficacy of quinidine (broad-spectrum potassium channel blocker) in patients with EIMFS. Unblinded assessment of seizure reduction may range from complete to no response.[12-17] Overall, half of EIMFS or EOEE patients will have no response to quinidine, and only 20% may benefit with at least a 50% seizure reduction.[18] The main adverse effect attributed to quinidine therapy is cardiotoxicity with prolonged QTc interval and arrhythmias, but sedation, elevated liver function tests, rash, and skin discoloration have also been described.[18,19]

We sought to evaluate the clinical aspects including phenotypic presentation, EEG, neuroimaging, response to pharmacological and non-pharmacological therapies of a multiethnic cohort of children with pathogenic or likely pathogenic *KCNT1* variants. Despite the high pleiotropy and heterogeneity associated with KCNT1-related epilepsies, we also aimed to explore any possible phenotype-genotype correlations associated with the most common identified variants.

METHODS

Patients and Institutional Review Board Approval

Ethics approval for the study was granted by the Research Ethics Board at The Hospital for Sick Children, Toronto, Ontario, Canada (REB #1000061319) and the other participant centres, as per the respective hospital policies. Children were enrolled in the study after consent was obtained from legal guardians, unless the local board institution waived the need to obtain an informed consent from a given center. Recruitment started within the Division of Neurology at the Hospital for Sick Children, which was the coordinating research site. Henceforth, an international collaborative network joined the study allowing us to recruit patients from Brazil, Canada, India, Israel, Saudi Arabia, and the United States. All mutations were identified by commercial gene panels or whole exome sequencing.

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Study Design, Inclusion and Exclusion Criteria

Inclusion criteria for this retrospective case series study were: (I) age 18 years or younger, (II) diagnosed with KCNT1-related epilepsy at any point until September 2018, (III) patients with pathogenic or likely pathogenic *KCNT1* variants (Class 5 or 4), according to The American College of Medical Genetics and Genomics (ACMG)[20,21], regardless of the phenotypic presentation. The exclusion criteria were: (I) patients harboring *KCNT1* variants of uncertain significance (VUS) or benign variants, and (II) failure to gather enough data for phenotypic characterization.

Data collection, analysis and interpretation

Study data were collected, stored and managed using REDCap (Research Electronic Data Capture) secure electronic data capture tool at The Hospital for Sick Children.[22,23] Data abstraction protocol included: demographics, age of presentation, first symptom developed by the patient, age of seizure onset, seizure type(s), presence of known epilepsy syndrome, developmental history, neurological/psychiatric/systemic comorbidities, genotype and inheritance (if available), EEG reports, neuroimaging abnormalities and pharmacological and non-pharmacological treatment and treatment response. For each treatment modality, the following options were gathered from caregivers and clinicians: (I) seizure freedom; (ii) marked improvement (i.e. greater than 50% reduction in seizures); (III) some improvement (i.e. 25-50% seizure reduction); (IV) minimal improvement (i.e. less than 25% seizure reduction); (V) no improvement; and (VI) worsening of seizures. In addition, tolerability, adverse effects, reason for discontinuation of therapy, and duration of therapies were gathered. Data were summarized using descriptive statistics, including mean, median, range and standard deviation (SD) for continuous variables and percentages for categorical variables.

Clinical genetic testing (i.e. through gene panels or whole exome sequencing) was performed through different companies internationally, using their specific protocols to obtain genomic DNA from blood. Testing of family members was performed according

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to clinical indication and/or availability using Sanger sequencing in nearly all cases. Variants of unknown significance, benign and likely benign variants in other genes, as well as heterozygous pathogenic variants detected in genes associated with autosomal recessive conditions were considered out of the scope of the study and will not be reported.

To address the second aim of the study (i.e. to determine phenotype-genotype correlations associated with more frequently encountered variants), we performed the Chi-square test (IBM SPSS statistics version 20.0 Armonk, NY: IBM Corp.) to compare the presence of specific findings (such as developmental plateauing, presence of EIMFS, reported seizure frequency greater than 500/month, abnormal MRI) in the most frequently encountered *KCNT1* variants found in our cohort (i.e. 2800G>A; p.Ala934Thr and c.862G>A; p.Gly288Ser). In addition, the Chi-square test was used to compare children with and without these variants, with respect to treatment responses to quinidine, diet therapy, and CBD. Moreover, given the previous literature data suggesting that an earlier age of onset of quinidine therapy could result in a better response, we compared the age of initiation of quinidine therapy to the seizure reduction response using Spearman's Rho calculator. Statistically significant correlations were considered positive if $P < .05$.

All data were reviewed by two authors from the main research site for completeness; whenever incomplete or unclear information was noted, further clarification was sought from the contributing centre. Individual genetic results (*KCNT1* variants) obtained from each center were checked and re-classified (if required) in accordance with the ACMG criteria.[20,21] If, on re-classification, patients were found to have VUS or benign variants, they were then subsequently excluded from the analysis.

RESULTS

Thirty children were initially recruited from all centers. However, three patients were excluded upon review, as their *KCNT1* variants were classified as VUS. Our cohort was

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composed of 27 children, 15 males and 12 females (ratio 1.25), current mean age 40.8 months (SD 28.3, median 38 months). Three patients were previously published (case# 15, case#16, and case #25)[24, 25] and 24 children are newly reported. For all children, seizures were the first concern that brought them to attention of a neurologist, with age of onset of seizures ranging from one day to six months of life (mean 1.7 months, SD 1.7, median 1 month). Nevertheless, the mean age for a definitive diagnosis of KCNT1-related epilepsy was later and only at mean of 18.8 months, SD 20.1 (median 10 months). Developmental trajectory was characterized by plateauing in nearly half of children (48.1%, 13/27) upon seizure onset, whereas 22.2% (6/27) had slow developmental gains, and 22.2% (6/27) had developmental regression, followed by either slow gains or plateauing.

Recurrent *KCNT1* variants were reported in 18 patients. The most common *KCNT1* variants were (i) c.2800G>A; p.Ala934Thr; (ii) c.862G>A; p.Gly288Ser; and (iii) c.1421G>A; p.Arg474His. These variants were respectively seen in five (cases #4, #8, #16, #24, and #27), four (cases #7, #9, #10, and #11), and three (cases #6, #17, and #20) children. In addition, (iv) c.1283 G>A; p.Arg428Gln (cases #1 and #23); (v) c.1420C>T; p.Arg474Cys (cases #13 and #22); and (vi) c.2849G>A; p.Arg950Gln (cases #3 and #15) were found in two children each. From the nine non-recurrent *KCNT1* variants found in this cohort, four have not been previously reported in the literature (cases #2, 12, #14, and #18). Case 12's nucleotide variant (c.1130G>C) is novel, however a nucleotide variant affecting the same amino acid (c.1129T>A; p.Cys377Ser) has been reported in a patient presenting with EIMFS.[26]

Parental testing was completed in 24 out of the 27 families, and 23 children (95.8%, 23/24) were found to have *de novo* variants. Despite having a *de novo* variant, six out of the 23 children (26%, 6/23) with a *de novo* variant had a positive family history of seizures. We had only limited information to the specific epilepsy syndromes in the affected relatives: (i) case 3's maternal great uncle had unclassified epilepsy; (ii) three third cousins of case 9 had recurrent seizures in adulthood; (iii) case 14's grandmother had unprovoked seizures in adulthood and this maternal grandmother's sister had febrile seizures in childhood; (iv) case 15's paternal grandfather's brother had seizures

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in childhood only; (v) a paternal first cousin of case 16 had seizures, and there is also a history of febrile seizures in this patient's second cousins; finally (vi) case 26's father had recurrent seizures attributed to a previous history of traumatic brain injury. Only one child (case #10) presented with an inherited variant from an unaffected parent. Case 10's mother has no neurological manifestations, but is heterozygous for the variant c.862G>A; p.Gly288Ser. Consanguinity was reported in four families from Saudi Arabia, cases #5, #6, #7 and #8, and three out of these four variants (c.1885A>G, p.Lys629Glu; c.862G>A, p Gly288Ser; and c.2800 G>A; p.Ala 934Thr) were found to be *de novo*. Parents of case #6 were not available for testing (unknown inheritance of the variant c.1421G>A; p.Arg474His)

EIMFS was the most common electroclinical syndrome, present in 18 patients (66.7%, 18/27). Four children had an unclassified EOEE, three children were diagnosed with West syndrome, and two children were diagnosed with ADSHE at some point. Three children have had more than one electroclinical phenotype throughout their trajectories: cases #3 and #4 initially presented with EIMFS evolving to West syndrome, whereas case #22's phenotype was initially consistent with unclassified EOEE, but later on developed ADSHE. Table 1 summarizes the demographics, relevant clinical information, KCNT1 variants details, and neuroimaging findings.

Focal impaired awareness motor (tonic, or with tonic component) seizures were the most common seizure type (48.1%, 13/27) observed in our cohort. In addition, a variety of other seizures were also observed such as: focal impaired awareness non-motor (behavioural arrest, autonomic, emotional), focal impaired awareness motor (hyperkinetic, clonic), generalized tonic, generalized tonic-clonic, generalized myoclonic-tonic-clonic, generalized myoclonic, and generalized absence seizures (atypical). Estimated current seizure frequency reported by caregivers was markedly variable at the time of data collection, with three patients (11.1%, 3/27) having more than 500 seizures/month, nine patients (33.4%, 9/27) having more than 100 and up to 500 seizures/month, three patients (11.1%, 3/27) having more than 50 up to 100 seizures/month, seven patients (26%, 7/27) having 10 to 50 seizures/month, and five

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patients (18.5%, 5/27) having less than 10 seizures/month. None of the caregivers reported seizure freedom.

The presence of developmental plateauing, EIMFS, and seizure burden were not associated with a specific genetic variant. Five children harboring c.2800G>A; p.Ala934Thr were compared to the rest of the cohort with respect to the presence of developmental plateauing (*P*=.13) phenotype consistent with EIMFS (*P*=.48), and estimated seizure frequency greater than 500 per month (*P*=.22). In addition, four children harboring c.862G>A; p.Gly288Ser were compared to the rest of the cohort with respect to the presence of developmental plateauing (*P*=.93) phenotype consistent with EIMFS (*P*=.44), and estimated seizure frequency (*P*=.38). There were no significant differences between the genotypes analyzed compared the rest of the cohort with respect to the aforementioned characteristics. The most common phenotype seen in our cohort consisted of non-ambulatory (92.3%, 24/26; unavailable data in one patient), nonverbal (88%, 22/25; unavailable data in two patients), hypotonic (74%, 20/27) and spastic (48.1%, 13/27) patients, with acquired microcephaly (65.3%, 17/26; unavailable data in one patient) and cortical visual impairment (60%, 15/25; unavailable data in two patients). Only five children (18.5%, 5/27) were diagnosed with involuntary movements (see Table 1).

Brain MRI was abnormal in the majority of children (59.3%, 16/27). The most common findings were delayed myelination (68.7%, 11/16; or 40.7%, 11/27 of all patients), thin corpus callosum (43.7%, 7/16; or 26%, 7/27 of all patients), usually but not always accompanied by brain atrophy (37.5% 6/16; or 22%, 6/27 of all patients). The presence of an abnormality in the brain MRI was further evaluated in the two most common genetic variants in comparison to the rest of the cohort. There was no correlation between the presence of an abnormality in patients with specific genotypes in comparison to the rest of the cohort (i.e. c.2800G>A; p.Ala934Thr versus other patients, *P*= .97; c.862G>A; p.Gly288Ser versus other patients, *P*=.68).

Systemically, these children often had constipation (40.7%, 11/27), gastroesophageal reflux disease (33.4%, 9/27), and aspiration pneumonia (33.4%, 9/27). Only one child

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(case #7) had a cardiac malformation (ventricular septal defect) and supraventricular ectopic activity.

Table 2 shows the current AEDs, number of total AEDs tried for each patient, alternative therapies and estimated response for each, and final disposition for each patient. Twenty-three children are still under follow up (85.2%, 23/27) and four passed away (14.8%, 4/27). Cause of death was due to complications of systemic diseases (n=1), progression of illness (n=1), and redirection of the goal of care (n=2). There were no reports of sudden unexpected death in epilepsy (SUDEP). Out of the 23 children being followed, the number of current anti-epileptic drugs (AEDs) in use ranged from one to five (mean 2.7, SD 1.2, median 2). Including the patients who died, the total number of AEDs tried ranged from three to 16 (mean 7.4, SD 3.1, median 7). Given the high number of medications tried in a relatively short period of time, subjective nature of responses, along with a variety of different combinations, we were unable to identify one or two AEDs that were particularly effective in controlling seizures. Eleven patients were tried on quinidine, with doses ranging from 20 to 60mg/kg/day (mean 35.9 mg/kg/day, SD 11.1, median 40 mg/kg/day) and duration of therapy from one to 28 months (mean 9.1 months, SD 9.5, median 4 months). As per caregivers, estimated response was marked or some improvement in five (45.4%, 5/11), but no response whatsoever in six children (54.6%, 6/11). Five children (45.4%, 5/11) developed QTc prolongation while on quinidine, but none discontinued therapy for this reason. Irritability and vomiting were reported in one child each. The age at administration of quinidine ranged from two to 37 months (mean 11.4 months, SD 9.8, median 8 months). There was no statistically significant correlation between responses to quinidine and the earlier age of onset of therapy (rs = .22917, *P* (2-tailed) = .49).

Cannabidiol (CBD) was used in seven patients (26%, 7/27), with highly variable doses ranging from 0.25 to 10 mg/kg/day (mean 6 mg/kg/day, SD 4.4, median 7.5 mg/kg/day). Estimated response was reported as marked or some improvement in five children (71.4%, 5/7), and minimal in two (28.6%, 2/7). CBD was well tolerated in all patients, with no side effects reported by the caregivers. Diet therapies were tried in fourteen patients (51.8%, 14/27), which included the ketogenic diet in twelve and low glycemic

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index diet in two. Eight children (57.2%, 8/14) had marked or some improvement, and six (42.8%, 6/14) had minimal or no improvement. There was no statistically significant correlation when children harboring c.2800G>A; p.Ala934Thr or c.862G>A; p.Gly288Ser were compared to the rest of the cohort, with respect to treatment response to quinidine, CBD, or diet therapy.

DISCUSSION

This observational study is one of the largest international cohorts examining pediatric patients diagnosed with KCNT1-related epilepsy. There was no selection bias with respect to the phenotypic characterization of this patients' sample, given that the essential criterion was related to the presence of pathogenic or likely pathogenic *KCNT1* variants. Some may argue that the presence of ADSHE could be underestimated due the cut-off age of the inclusion criteria, but we believe our data reflects the current circumstances of clinicians dealing with KCNT1-related epilepsy in infancy and childhood. The 17-month gap between first seizures (i.e. mean age at onset of seizures 1.7 months) and diagnosis of KCNT1-related epilepsy (mean age at diagnosis 18.8 months) in our cohort reflects the true odyssey for families and physicians alike.

As previously reported by different authors, *KCNT1* pathogenic variants are highly pleiotropic and associated with a variety of phenotypes.[8,18,27] In our study, two-thirds of patients presented with EIMFS, however, unclassified EOEE, West syndrome and ADSHE were also present, similar to previous reports. Further analysis of recurrent variants and seizure burden related to specific genotypes was not significant, reinforcing the variability in gene expression and high pleiotropy of *KCNT1* pathogenic variants.

However, our data obtained from 27 affected children enabled us to refine the phenotypic characterization, which may help in earlier recognition of these patients: early onset of tonic seizures which are medically refractory, with plateauing of milestones, hypotonia, cortical visual impairment, and acquired microcephaly should promptly raise a heightened index of suspicion for KCNT1-related epilepsy, likely

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manifesting as EIMFS or unclassified EOEE. Obviously, other seizure types and developmental trajectories can be seen. Similar to our results, the high prevalence of acquired microcephaly was also noted by Kuchenbuch et al. as high as 90% after three years of follow up.[28] Given the cross-sectional nature of our study, we were not able to delineate different phases experienced by EIMFS patients over time, recently described as stormy phase, stabilization period, and chronic phase.[28]

Somatic mosaicism (i.e. DNA alteration occurring at the post-zygotic stage) may also contribute to the phenotypic heterogeneity seen in some epilepsy genes. As previously demonstrated for "*de novo*" epileptic encephalopathies, 8.3% of parents have mosaicism of their child's pathogenic variant, particularly when there is parental history of seizures.[29] Interestingly, the high prevalence of positive family history of seizures (~ 30%) in our patients and in another study[28] might indicate the need for future research focused on relatives of patients with KCNT1-related epilepsy.

Although we often consider that neuroimaging is normal in the genetic epileptic encephalopathies, our data strengthen that in KCNT1-related epilepsies brain MRI can be abnormal (59% of our children). From those with abnormal imaging, we found that delayed myelination, thin corpus callosum, and brain atrophy were the most common findings, albeit some of these abnormalities (i.e. delayed myelination and brain atrophy) are likely depending whether the neuroimaging was obtained at earlier or later stages of the disease. One of our patients (case #27) was found to have areas of indistinctness in the grey-white matter interface, which could suggest an underlying malformation of cortical development, as recently described in patients with KCNT1 pathogenic mutations and ADSHE.[11]

Given the expression of *KCNT1* in muscle tissue, gonads, and the pituitary gland, it has been proposed that *KCNT1* mutations can be involved in cardiac anomalies, SUDEP, and precocious puberty.[5,27,28] Indeed, one of our patients (case#7) was diagnosed with a ventricular septal defect, and supraventricular ectopic activity. However, unlike in the other reported cases, neither SUDEP nor precocious puberty were reported in our series, possibly due to limited long term follow up of this cohort. A cross-sectional study including older patients as well as long term follow up assessments could help

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identifying precocious puberty and, perhaps, SUDEP if these conditions are related to KCNT1-related epilepsy.

Poor response to AEDs is a common characteristic among KCNT1-related epilepsy patients regardless of the phenotype. Not different from other studies,[18,28] our patients were exposed to several AEDs over time (mean 7.4, SD 3.1), with no seizure freedom achieved. Moreover, more than half (55%, 15/27) reported more than 50 seizures monthly. These data promptly led to clinicians and families to look for alternative treatments. After some case reports successfully reported treating KCNT1-related epilepsy with quinidine,[12,13] several authors unfortunately have not been able to reproduce the same outcomes.[14-17] In addition, a small blinded, placebo-controlled, crossover trial that included six ADSHE patients did not show significant difference in seizure frequency during the quinidine phase compared to placebo, and paroxysmal arousals were similarly unchanged. There were no patients achieving the 50%-reduction mark.[30]

In our retrospective analysis, nearly 50% of (5/11) patients had marked or some seizure reduction with quinidine. Twenty-seven percent (3/11) reported greater than 50% seizure reduction and 18.1% (2/11) reported from 25 to 50% seizure reduction. Our findings were similar to those from the largest cohort of KCNT1-related epilepsy that evaluated 20 patients taking quinidine and found nearly 50% (9/20) of patients with some response, including 20% of patients having at least 50% seizure reduction.[18] Neither seizure freedom nor worsening of seizures was reported in our patients. In addition, we were not able to establish statistical correlation suggesting an age-dependent response to quinidine, as previously reported in the literature.[15]

Other than quinidine, we were also able to record reasonable efficacy of diet therapy and CBD. When taking into consideration patients exposed to diet therapies, 43% (6/14) had greater than 50% seizure reduction. Analyzing the response to the ketogenic diet (not including the low glycemic index diet), half of the patients (6/12) had greater than 50% seizure reduction. Reasonable response to the ketogenic diet has also been reported, with a response rate of 31% (9/29) as per caregivers and physicians.[18] For

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those who responded well to CBD, two out of three were previously on the ketogenic diet making any conclusions of the CBD efficacy merely speculative. In addition, the small number of patients on CBD and the lack of consistency of the dosage prescribed (from 0.25 to 10 mg/kg/day) limit our capacity to draw meaningful conclusions.

In addition to the limitations related to our study method, which include missing data and lack of longitudinal follow up, our study is hampered by the limited number of patients for subset analysis. This is difficult to overcome when gathering data in a rare condition. Parental reports of seizure frequency (sometimes hard to recognize due to subtle manifestations, or sometimes overcalled due to the presence of abnormal movements and behavioral issues) as well as the lack of standardized use of some therapies (i.e. CBD and quinidine doses) are further limitations of our study. Moreover, with our current data it is still unclear whether somatic mutations are particularly relevant in KCNT1-related epilepsy or not. Low level of parental mosaicism could be underestimated given that the great majority of parental testing in our study was through Sanger sequencing, and not through next generation sequencing analysis.[31]

In summary, through international collaboration and in comparison with previous literature data, we were able to delineate the common aspects within this highly pleiotropic entity, KCNT1-related epilepsy: early-onset refractory tonic seizures, likely (but not exclusively) manifesting as EIMFS or unclassified EOEE, along with milestones plateauing, hypotonia, cortical visual impairment, and acquired microcephaly. Supportive but not mandatory neuroimaging findings included delayed myelination, thin corpus callosum, brain atrophy, and rarely malformations of cortical development. Despite the lack of satisfactory evidence, alternative treatments such as the ketogenic diet and quinidine seem to be well tolerated and may help achieving seizure reduction greater than 50%.

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DISCLOSURE OF CONFLICTS OF INTEREST

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ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Key Point Box

- KCNT1-related epilepsy in children usually manifests as early-onset refractory focal tonic seizures and EIMFS.
- Most children will become non-ambulatory, nonverbal, hypotonic, spastic, with acquired microcephaly and cortical visual impairment.
- Supportive MRI findings include: delayed myelination, thin corpus callosum, brain

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atrophy, and malformations of cortical developmental.

- There have been no well-stablished genotype-phenotype specific correlations so far.
- Despite the lack of evidence-based practice, ketogenic diet and quinidine are well tolerated and may help with seizure reduction.

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Table 1 – Demographics, phenotype, genotype, and neuroimaging findings

Case#/ Sex/ Age at inclusion (m)/Origin	Seizure onset (m)	Age at genetic diagnosis (m)	KCNT1 variant and inheritance	Estimated seizure frequency /month[A]	Seizure type(s)[B]	Electroclinical syndrome(s)[C]	Developmental trajectory	Dysmorphism, neurological and psychiatric manifestations	Brain MRI	Additional features
1/ F/ 16 / Canada	1.5	5	De novo c.1283 G>A, p.Arg428Gln	> 500	FIAM (tonic), GT, GTC	EIMFS	Slowly ascending	Postnatal microcephaly, nonverbal, non-ambulatory, hypotonic, spastic on exam, cortical visual impairment	Delayed myelination	Aspiration pneumonia, GERD, G-tube fed
2/ M/ 21/ Canada	0.1	9	De novo c.1438G>A, p.Asp480Asn[D]	> 500	FIAM (tonic & clonic), GT	EIMFS	Plateauing	Postnatal microcephaly, nonverbal, non-ambulatory, involuntary movements, hypotonic, spastic on exam, cortical visual impairment	Delayed myelination, thin CC	GERD, G-tube fed
3/ M/ 67/ Canada	1.5	28	De novo c.2849 G>A; p.Arg950Gln	< 10	GTC, GT, FIANM (behavioral arrest)	EIMFS, WS	Regression > plateauing	Postnatal microcephaly, nonverbal, non-ambulatory, involuntary movements, hypotonic, spastic on exam	Cerebral atrophy, delayed myelination, thin CC	Aspiration pneumonia, constipation, GERD, G-tube fed
4/ F/ 59/ Canada	0.7	32	De novo c.2800 G>A, p.Ala934Thr	< 10	GT	EIMFS, WS	Plateauing	Postnatal microcephaly, nonverbal, non-ambulatory, hypotonic, cortical visual impairment	Cerebral atrophy, delayed myelination, thin CC	Aspiration pneumonia, constipation, GERD, G-tube fed
5/ F/ 72/ Saudi Arabia	1	24	De novo c.1885A>G, p.Lys629Glu	101-500	GMTC	EIMFS	Regression	Postnatal microcephaly, nonverbal, non-ambulatory, hypotonic	Cerebral atrophy, delayed myelination, thin CC	_
6/ M/ 48/	3	24	Unknown	10-50	GTC	EIMFS	Regression	Prominent forehead,	Cerebral	_

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Saudi Arabia			inheritance c.1421G>A, p.Arg474His					hypertelorism, nonverbal, non-ambulatory, hypotonic, spastic on exam	atrophy, delayed myelination, thin CC	
7/ F/ 30/ Saudi Arabia	2	6.5	De novo c.862G>A, p Gly288Ser	10-50	FIAM (tonic), FIANM (behavioral arrest)	EIMFS	Plateauing	Postnatal microcephaly, nonverbal, non-ambulatory, hypotonic, cortical visual & hearing impairment	Verticalized splenium of the CC	Cardiac arrhythmia, PFO, VSD
8/ F/ 75/ Saudi Arabia	5	55	De novo c.2800 G>A, p.Ala 934Thr	10-50	FIAM (tonic)	EIMFS	Plateauing	Postnatal microcephaly, nonverbal, non-ambulatory, hypotonic, spastic on exam	Cerebral atrophy, delayed myelination, thin CC	Constipation
9/ M/ 39/ Brazil	6	20	De novo c.862G>A, p.Gly288Ser	51-100	GT	None	Regression	Nonverbal, non-ambulatory, hypotonic, spastic on exam, cortical visual impairment	Normal	Constipation, GERD, G-tube fed
10/ M/ 38/ Israel	4	34	Maternally inherited c.862G>A, p.Gly288Ser	< 10	GTC, GT	WS	Slowly ascending	Brachycephalic, synophrys, deep set eyes, up-slanting palpebral fissures, midfacial hypoplasia, broad thumbs, postnatal microcephaly, nonverbal, non-ambulatory, hypotonic, involuntary movements on exam	Normal	_
11/ M/ 13/ Israel	1.5	4	De novo c.862G>A, p.Gly288Ser	10-50	FIAM (focal to bilateral TC), GTC	EIMFS	Plateauing	Coarse facial features, nonverbal, non-ambulatory, hypotonic	Unilateral widening of sylvian fissure	Aspiration pneumonia, constipation, G-tube fed
12/ F/ 46/ Saudi Arabia	1	11	De novo c.1130G>C, p.Cys377Ser[D]	101-500	FIAM (tonic), GTC	Unclassified EOEE	Plateauing	Postnatal microcephaly, nonverbal, non-ambulatory, hypotonic, spastic on exam,	Delayed Myelination	GERD, constipation, G-tube fed

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								cortical visual impairment		
13/ F/ 15/ India	0.3	6	Unknown inheritance c.1420C>T, p.Arg474Cys	> 500	FIAM (tonic)	EIMFS	Never gained milestones	Nonverbal, non-ambulatory, hypotonic, cortical visual impairment	Normal	_
14/ M/ 44/ India	1	4	De novo C.2885T>T/C, p.Leu962Pro[D]	101-500	FIAM (tonic)	EIMFS	Plateauing	Postnatal microcephaly, nonverbal, non-ambulatory, spastic on exam, cortical visual impairment	Normal	Aspiration pneumonia
15/ M/ 38/ India	0.5	7	De novo c.2849G>A, p.Arg950GIn	10-50	FIAM (automatisms & tonic)	EIMFS	Slowly ascending	Postnatal microcephaly, autistic, nonverbal, non-ambulatory, hypotonic, involuntary movements on exam	Normal	_
16/ M/ 28/ India	0.3	5	De novo c.2800 G>A, p.Ala934Thr	51-100	FIAM (clonic)	EIMFS	Plateauing	Plagiocephaly, postnatal microcephaly, nonverbal, non-ambulatory, hypotonic, cortical visual impairment	Normal	Aspiration pneumonia, G-tube fed
17/ M/ 96/ USA	3	57	De novo c.1421G>A, p.Arg474His	< 10	FIAM (hyperkinetic)	ADSHE	Slowly ascending	Behavioral issues, language delay, hypotonic	White matter changes	Constipation
18/ M/ 19/ India	2	10	De novo c.255G>C; p.Arg85Ser[D]	101-500	FIANM (autonomic & behavioral arrest)	Unclassified EOEE	Slowly ascending	Postnatal microcephaly, nonverbal, non-ambulatory, hypotonic, cortical visual impairment	Delayed myelination	_
19/ F/ 34/ India	0.03	14	De novo c.820C>A, p.Leu274Ile	101-500	FIANM (behavioral arrest), FIAM (tonic)	EIMFS	Plateauing	Postnatal microcephaly, nonverbal, non-ambulatory, hypotonic, spastic on exam, cortical visual impairment	Normal	Constipation

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20/ F/ 13/ Canada	0.5	6	De novo c.1421G>A, p.Arg474His	101-500	FIAM (tonic & clonic)	EIMFS	Plateauing	Nonverbal, non-ambulatory, hypotonic, cortical visual impairment	Delayed Myelination	Aspiration pneumonia, constipation, GERD
21/ F/ 66/ India	3	37	Unknown inheritance c.2882G>G/A, p.Arg961His	101-500	FIAM (tonic), GM, GA (atypical)	Unclassified EOEE	Regression > slowly ascending	Postnatal microcephaly, autistic, behavioral issues, nonverbal, non-ambulatory, involuntary movements, spastic on exam, cortical visual impairment	Cerebral atrophy, delayed myelination, thin CC	_
22/ M/ 125/ India	1	84	De novo c.1420C>T, p.Arg474Cys	< 10	FIAM (clonic), UNM (behavioral arrest)	Unclassified EOEE, ADSHE	Slowly ascending	Elongated facies, inverted V-shaped upper lip, smooth philtrum, high arched palate, small ears, autistic, behavioral issues, language delay	Increased perivascular spaces	_
23/ M/ 29/ India	1	4	De novo c.1283 G>A, p.Arg428Gln	10-50	FIANM (emotional)	EIMFS	Plateauing	Palpebral upslant, long philtrum, postnatal microcephaly, behavioral issues, nonverbal, non-ambulatory, spastic on exam, cortical visual impairment	Normal	Constipation, GERD
24/ M/ 38/ India	1	6	De novo c.2800 G>A, p.Ala934Thr	101-500	FIAM (tonic), GT	Unclassified EOEE	Plateauing	Postnatal microcephaly, behavioral issues, nonverbal, non-ambulatory, spastic on exam	Normal	Aspiration pneumonia
25/ M/ 9/ India	0.1	4	De novo c.808 C>G. p.Gln270Glu	101-500	FIANM (autonomic)	EIMFS	Not available	Sloping forehead, long philtrum, thin upper lip, long slender fingers, spastic on exam	Normal	Aspiration pneumonia

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26/ F/ 21/ USA	5.5	10	De novo c.1193G>A; p.Arg398Gln	10-50	FIAM (clonic & tonic)	None	Plateauing	Language delay, non-ambulatory	Normal	Constipation, GERD
27/ F/ 5/ USA	0.1	2	De novo c.2800G>A, p.Ala934Thr	51-100	FIAM (clonic), FIANM (behavioral arrest & autonomic)	EIMFS	Regression	Non-ambulatory, hypotonic, cortical visual impairment	R frontal-parietal and L parietal areas of indistinctness grey- white interface.	_

Abbreviations: ADSHE: autosomal dominant sleep-related hypermotor epilepsy; CC: corpus callosum; EIMFS: epilepsy of infancy with migrating focal seizures; EOEE: Early onset epileptic encephalopathy; F: female; FIAM: focal impaired awareness motor onset; FIANM: focal impaired awareness non-motor onset; GERD: Gastroesophageal reflux disease; GA: generalized absence; GT: generalized tonic; GMTC: generalized myoclonic-tonic-clonic; GTC: generalized tonic-clonic; L: left; M: male; m: months; PFO: patent foramen ovale; R: right; UNM: unknown non-motor onset; VSD: ventricular septal defect; WS: West syndrome.

A: As per parental/caregiver reports.

B: Electroclinical syndromes were diagnosed based not only on the current seizure types, but also past seizures and electrographic correlations.

C: Current seizure types are listed from the most frequently to the last frequently observed by parents/caregivers.

D: Previously unreported, novel variant. Of note: The nucleotide variant c.1130G>C is novel (case#12), albeit a nucleotide variant affecting the same amino acid (i.e. c.1129T>A; p.Cys377Ser) has been reported in a patient presenting with EIMFS.[26]

Table 2 – Current and past therapies, estimated response to alternative treatments, and final disposition.

Case#	Current AEDs	Number of past/total AEDs tried	Diet therapy/ duration (m)/ Maximum ratio/ Estimated response*	Quinidine therapy/ duration (m)/ Maximum dose[#]/ Estimated response*	CBD therapy/ duration (m)/ Maximum dose/ Estimated response*	Final disposition
1	CLB, LRZ, PB	6/ 9	KD/ 9/ 4:1/ marked	Y/ 1/ 40mg/kg/day / nil	Y/ 8/ 10mg/kg/day/ some	Under follow up
2	PB	5/ 6	KD/ 6/ 3.75:1/ nil	Y/ 3/ 60mg/kg/day / nil	Y/ 1/ 10mg/kg/day/ some	Under follow up
3	LEV, PB	7/9	KD/ 49/ 4.25:1/ marked	Not tried	Y/ 31/ 7.5mg/kg/day/ marked	Under follow up

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4	LEV	2/ 3	KD/ 46/ 4:1/ marked	Not tried	Y/ 8/ 0.5mg/kg/day / marked	Under follow up
5	N/A	9/ 9	Not tried	Not tried	Not tried	Died (systemic illness)
6	LEV, VPA	1/ 3	Not tried	Not tried	Not tried	Under follow up
7	LEV, TPM	2/ 4	Not tried	Not tried	Not tried	Under follow up
8	PB, TPM	2/ 4	Not tried	Not tried	Not tried	Under follow up
9	CLB, OXC, TPM	4/7	KD/ 21/ 4:1/ marked	Y/ 19/ 20mg/kg/day / some	Not tried	Under follow up
10	CLB, LEV, PB	4/ 7	KD/ 31/ 3:1/ marked	Y/ 3/ 40mg/kg/day / marked	Not tried	Under follow up
11	CBZ, CLN	10/ 12	KD/ 1/ 3:1/ nil	Y/ 9/ 40mg/kg/day / some	Y/ 9/ 10mg/kg/day/ marked	Under follow up
12	GBP, LEV, TPM, VGB	2/ 6	Not tried	Not tried	Not tried	Under follow up
13	CLB, LEV, PB, VPA	3/ 7	Not tried	Not tried	Not tried	Under follow up
14	LEV, PER, TPM, VPA	6/ 10	KD/ 0.5/ 3:1/ some	Not tried	Not tried	Under follow up
15	CLB, LEV, PB	3/ 6	LGID/ 30/ unknown/ some	Y/ 28/ 40mg/kg/day / marked	Not tried	Under follow up
16	CLB, PB, DPH, TPM	7/ 11	LGID/ 3/ N/A/ minimal	Y/ 22/ 20mg/kg/day / marked	Not tried	Under follow up
17	DZP	5/ 6	KD/ unknown/ 3.75:1/ marked	Not tried	Not tried	Under follow up
18	CLB, LEV	4/ 6	Not tried	Not tried	Not tried	Under follow up
19	ACTH, CLB, LEV, PB, TPM	6/ 11	KD/ 9/3:1/ minimal	Not tried	Y/unknown/ 4mg/kg/day/ nil	Under follow up
20	N/A	6/ 6	Not tried	Y/ 4/ 30mg/kg/day / nil	Not tried	Died (disease progression and redirection of care)
21	PIR, VPA	8/ 10	Not tried	Not tried	Not tried	Under follow up
22	CBZ, CLB, TPM	3/ 7	Not tried	Not tried	Not tried	Under follow up
23	CBZ, CLN, LEV, TPM, VPA	11/ 16	Not tried	Not tried	Not tried	Under follow up
24	LEV	9/ 10	Not tried	Not tried	Not tried	Under follow up
25	N/A	11/ 11	KD/ 1/ 3.5:1/ nil	Y/ 2/ 35mg/kg/day / nil	Not tried	Died (systemic illness)
26	CLN, LEV	2/ 4	Not tried	Y/ 9/ 30mg/kg/day / nil	Not tried	Under follow up
27	N/A	5/ 5	KD/ 2/ 4:1/ nil	Y/ 1/ 40mg/kg/day / nil	Y/ unknown/ 0.25mg/kg/day/ nil	Died (disease progression and redirection of care)

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Abbreviations: ACTH: adrenocorticotropic hormone; CBZ: carbamazepine; CLB: clobazam; CLN: clonazepam; DPH: Phenytoin; DZP: Diazepam; GBP: gabapentin; KD: ketogenic diet (classical); LEV: levetiracetam; LIGD: low glycemic index diet; LRZ: lorazepam; N/A: not applicable; OXC: oxcarbazepine; PB: phenobarbital; PER: perampanel, PIR: piracetam; TPM: topiramate; VGB: vigabatrin; VPA: valproate; Y: yes. *Estimated response scale: marked improvement: > 50% reduction in seizures; some improvement: 25-50% reduction in seizures; minimal: < 25% reduction in seizures; nil: no changes in seizure frequency.

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