

Early Initial Video-Electro-Encephalography Combined With Variant Location Predict Prognosis of KCNQ2-Related Disorder

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Abstract

Background: The clinical features of *KCNQ2*-related disorders range from benign familial neonatal seizures 1 to early infantile epileptic encephalopathy 7. The genotype-phenotypic association is difficult to establish.

Objective: To explore potential factors in neonatal period that can predict the prognosis of neonates with *KCNQ2*-related disorder.

Methods: Neonates with *KCNQ2*-related disorder were retrospectively enrolled in our study in Children's Hospital of Fudan University in China from Jan 2015 to Mar 2020. All patients were older than age of 12 months at time of follow-up, and assessed by Bayley Scales of Infant and Toddler Development-Third Edition (BSID-III) or Wechsler preschool and primary scale of intelligence-fourth edition (WPPSI-III), then divided into three groups based on scores of BSID-III or WPPSI-III: normal group, mild impairment group, encephalopathy group. We collected demographic variables, clinical characteristics, neuroimaging data. Considered variables include gender, gestational age, birth weight, age of the initial seizures, early interictal VEEG, variant location, delivery type. Variables predicting prognosis were identified using multivariate ordinal logistic regression analysis.

Results: A total of 52 neonates were selected in this study. Early interictal video-electro-encephalography (VEEG) (OR=2.77; 95%CI: 1.20-6.34, P=0.001), and variant location (OR=2.77, 95%CI: 0.03-5.50, P=0.048) were independent risk factors for prognosis ($p < 0.05$).

Conclusions: The integration of early initial VEEG and variant location can predict prognosis. An individual whose *KCNQ2* variant located in voltage sensor, the pore domain, with worse early initial VEEG background, often had an adverse outcome.

Background

KCNQ2 encodes a voltage-gated potassium channel protein, reciprocally with *KCNQ3* to form a potassium channel with essentially identical properties to the channel underlying the native M-current. *KCNQ2*-related disorders represent a broad continuum of epileptic phenotypes caused by a heterozygous variant in *KCNQ2*. The clinical features of *KCNQ2*-related disorders range from mild forms, as benign familial neonatal seizures 1 (BFNS1, [MIM:121200]), to very severe ones, as early infantile epileptic encephalopathy 7 (EIEE7, [MIM:613720]). *KCNQ2*-related disorder is generally characterized by multiple daily seizures that usually occurs between the first to eighth day of life^[1-12], rare cases at few months of life^[4-7]. Seizure types are mostly tonic or apneic episodes, focal clonic activity, or autonomic changes^[1-12].

Generally, individuals with identical pathogenic variants appear similar clinical features and developmental outcomes, but some cases exhibit clinical heterogeneity. For example, one or more individuals who developed a therapy-resistant epileptic encephalopathy have been observed in families

with BFNS1^[13-15]; the p.Arg213Trp *KCNQ2* pathogenic variant has been reported in an individual with severe epileptic encephalopathy^[16] and in another family with normal outcome^[17]. Heterogeneity of phenotype indicated the complex correlation with genotype.

Limited by number of cases, few studies focus on the relationship between clinical features, treatment and prognosis of *KCNQ2*-related disorder^[18-19]. We are seeking for some factors in neonatal period that can predict the long-term outcome, such as: interictal video-electro-encephalography (VEEG), date of onset, variant location, and so on.

Methods

Patients

We retrospectively recruited the neonates who had seizures within the first month of life in Children's Hospital of Fudan University in China from Jan 2015 to Mar 2020. Of all the patients with convulsions, we selected those have *KCNQ2* gene variants identified by molecular genetic testing and agreed to have VEEG examination during the neonatal period in our study. They were followed up to at least 12 months of age.

Genetic testing: Genomic DNA were extracted from peripheral blood. Whole exome sequencing (WES) or clinical exome sequencing (2742 targeted genes) was performed to identify mutations. We used public databases (the dbSNP137 reported in the UCSC Genome Browser, the exome aggregation consortium, and the 1000 Genome Project) and our local database to filter the variants. Sanger sequencing was performed to confirm the candidate variants. In this cohort, patients enrolled were met one of the following four criteria: 1) patients with a previously established heterozygous pathogenic variant in *KCNQ2* gene, which from both public database and internal database; 2) same amino acid change as a previously established pathogenic variant, however different nucleotide change; 3) patients with novel (both public database and internal database) heterozygous null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon) in *KCNQ2* gene; 4) patients with novel and de novo heterozygous variant in the negative family history; or inherited from the affected parents. All the genetic results were interpreted by two experienced molecular genetic clinicians simultaneously.

Previous studies showed that pathogenic variants in EIEE7 cluster in four functionally important protein domains: voltage sensor, the pore, C-terminus proximal region (important for modulation by second messengers), and calmodulin-binding B helix region^[11]. Common location of *KCNQ2*- encephalopathy missense variants reported by two recent studies cluster at voltage sensor (S4), the pore domain (from S5 to S6, including S5, S5-H5 linker, H5, H5-S6 linker, S6)^[20-21]. We selected common location as key spots.

We categorized the variant location of *KCNQ2*: 0, non-key spots; 1, key spots.

VEEG

Scalp EEGs were recorded at 8 electrodes (F3/F4, C3/C4, T3/T4, P3/P4,) according to the international 10–20 system using the Nicolet VEEG monitor (Nicoletone, Middleton, Wisconsin, United States). Each neonate had at least one VEEG recording. Each recording lasted more than 4 hours including at least one full cycle of wakefulness and sleep.

Most patients have been treated with anti-epileptic drugs(AEDs) in other hospitals. In order to reduce the deviation caused by AEDs, for the patients who have not used anticonvulsant drugs before, we use the VEEG data of more than 3 days after taking AEDs in our hospital as early interictal VEEG, while used the first VEEG data in our hospital for the patient who have been treated with AEDs in other hospital as early interictal VEEG.

Each VEEG data was read by two experienced neurophysiologists individually. If the results from the two neurophysiologists were consistent, they would directly apply it. If not, they would discuss together to give the final results. If they can't reach an agreement in the end, the data would be discussed by the VEEG team which including more than three more experienced neurophysiologists.

According to VEEG background classification, we divide VEEG into normal, mild abnormal, moderate abnormal, and severe abnormal^[22]. Moderately abnormal VEEG was divided into two groups according to whether the sleep cycle can be distinguished.

We assigned points according to the following conditions:

0 , normal

1, Mildly abnormal: mild multifocal sharp waves (Fig. 1.A);

2, Moderately abnormal: multifocal sharp waves,with sleep cycle (Fig. 1.B);

3, Moderately abnormal: multifocal sharp waves,without sleep cycle (Fig. 1.C);

4, Markedly abnormal: burst-suppression pattern (Fig. 1.D).

Delivery type

0, Vaginal delivery; 1, Cesarean section.

Other clinical data

Clinical manifestations, including gender, birth weight, age of the onset, and gestational age, of each proband were ascertained comprehensively through physician by the review of the medical records.

outcome

Prognosis referred to the prognosis of at least 12 months of follow-up. All patients were older than 12 months old at time of follow-up. The Bayley Scales of Infant and Toddler Development-Third Edition

(BSID-III) was used to assess the developmental level of patients between 12 and 42 months of age^[23]. A composite score below 70 (2SD below the mean) in the cognitive indicates moderate or profound developmental delay; a score in the cognitive below 85 (1SD below the mean) indicates mild impairment; a score in the cognitive of 100 or more indicates normal. The Wechsler preschool and primary scale of intelligence-fourth edition (WPPSI-IV) was used to assess the development level of children more than 42 months of age (normal (FSIQ (full scale IQ score) ≥ 70); mild (FSIQ 50-69); moderate or profound (FSIQ < 50)).

Prognosis was graded into four categories according to different evaluation scores:

0: normal group (any evaluation score was normal)

1: mild impairment group (any evaluation score was mild)

2: encephalopathy group (any evaluation score was moderate or profound, including patients with frequent convulsions and underdevelopment at the time of death)

Statistics: Normally distributed data are presented as mean \pm standard deviation (SD), skewed data are presented as medians (interquartile range).

Prognosis was regressed on predictors with ordinal logistic model. Considered variables include gender, gestational age, birth weight, age of the initial seizures, early interictal VEEG, variant location, delivery type. We modelled gestational age, birth weight, and age of the initial seizures as continuous variables, early interictal VEEG as ordinal variables, and variant location, and delivery type as categorical variables. Predictors significant at a level 0.05 in univariate analyses were entered into a multivariate model and retained at the significance level of 0.05. Statistical analysis was performed by SPSS statistics version 21.0.

Results

57 neonates (from Jan 2016 to Mar 2020) who had onset of seizures within the first month of life were enrolled. All of them carry *KCNQ2* gene pathogenic variants confirmed by molecular genetic testing in Children's Hospital of Fudan University. Three patients were excluded due to unavailable VEEG data in the neonatal period, and two patients were excluded because of lost to follow-up. (Fig. 2)

Of the 52 patients included, 23 (44.2%) were females. The clinical features and *KCNQ2* variation information are summarized in Table 1 and Table e.

Table 1
Demographic of the cohort

Participant characteristics	Category	Long-term outcome (n = 52)		
		Normal group (n = 17)	Mild impairment group (n = 2)	encephalopathy group (n = 33)
		Count (percentage)	Count (percentage)	Count (percentage)
Sex	Male	7 (41.18)	1 (50)	21 (63.34)
	Female	10 (58.82)	1 (50)	12 (36.36)
Birth weight(g)	Median (interquartile range IQR)	3350 (3045–3665)		3150 (2908–3600)
Gestational age	Median (IQR)	39.43 (39.00–40.00)		39.43 (38.00–40.00)
Age of initial seizures	Median (IQR)	3 (2.5-4.0)		2 (1.5–3.5)
Score of Early interictal VEEG	0	6 (35.29)	0	0
	1	5 (29.41)	1 (50)	0
	2	5 (29.41)	1 (50)	2 (6.06)
	3	1 (5.9)	0	10 (30.30)
	4	0	0	21 (63.64)
Variant location	Hotspots	3 (17.65)	1 (50)	22 (66.67)
	Non-hotspots	14 (82.35)	1 (50)	11 (33.33)
Delivery type	Vaginal delivery	9 (52.94)	1 (50)	16 (48.48)
	Cesarean section	8 (47.06)	1 (50)	17 (51.52)

Birth weight of the subjects was 3.31 ± 0.47 kg, with gestational age of 39.14 ± 1.41 weeks. The median date of initial seizures was 2.5 (IQR 2–4) days after birth of life. Half subjects were followed up after 24 (IQR 14–38) months of age (excluding two patients deceased). 43 patients between 12 and 42 months of age were assessed by BSID-III, 7 patients between 48 and 63 months of age were assessed by WPPSI-III, 2 patients who didn't undergo any detailed neurologic testing had frequent convulsions and underdevelopment at the time of death. 17 patients had normal development, 2 patients had mild impairment development, 33 patients had moderate/severe impairment development including 2 patients deceased. Univariable predictors are presented in the Table 2. Two variables including early interictal

VEEG and variant location were statistically significant associated with prognosis. The result of multivariate analysis was shown in the Table 2. The results of multivariate analysis showed that early interictal VEEG(OR = 2.77; 95%CI: 1.20~4.34, P = 0.001), and variant location(OR = 2.77, 95%CI: 0.03~5.50, P = 0.048) were independent risk factors for poor long-term outcome(p < 0.05).

Table 2
univariable analysis and multivariable Analysis

univariable analysis					Multivariable Analysis			
Variable	OR	SE	95%CI	P value	OR	SE	95%CI	P value
Early interictal VEEG	2.72	0.74	1.28~4.16	0.00	2.77	0.80	1.20~4.34	0.001
Variant location	2.06	0.67	0.75~3.38	0.00	2.77	1.40	0.03~5.5	0.048
Gender	-0.88	0.58	-2.02~0.26	0.131				
Birth weight(g)	-0.00	0.00	-0.00~0.00	0.143				
Gestational age	-0.14	0.21	-0.56~0.281	0.52				
Age of initial seizures	0.06	0.08	-0.09~0.21	0.43				
Delivery type	0.17	0.57	-0.95~1.29	0.77				

Discussion

Early interictal VEEG is statistically significant in judging prognosis. The VEEG of the time we selected may be more sensitive to the long-term outcome. For example, patient 34 had a refractory epileptic encephalopathy, the score of the first-time VEEG data was 3 without using any AEDs, while the score of the VEEG data seven days later was 4 after using phenobarbital; patient 5 had mild intellectual development, the score of the first time VEEG data was 3 without using any AEDs, while the score of the VEEG data five days later was 2 after using phenobarbital.

VEEGs of the patients with *KCNQ2*-related epileptic encephalopathy showed a BS pattern, hypsarrhythmia, or multifocal epileptiform activity in our study, which is similar to reported studies^[2, 4, 6-10, 12]. In patients with moderate or severe impairment development, the sleep cycle of the VEEG was indistinguishable. Multifocal epileptiform activity also can be observed in the patients of normal and mild impairment group, but the VEEGs show existing of sleep cycle. It is found that the more discharges, the higher early VEEG score (Fig. 1.A-D). Therefore, we speculate that the long-term outcome is positively correlated with the discharges of the early VEEG. In other studies, VEEG of patients with BFNS1 appears normal or rarely showing a pattern of "theta pointu alternant"^[1]. Interictal VEEG is useful for predicting long-term prognosis in our study. An article also revealed the ictal and interictal amplitude-integrated

electroencephalogram (AEEG) and EEG play a certain role in the diagnosis of *KCNQ2*-related disorder early, and showed diversity characteristics of EEG at different variant locations^[19].

Variant location (voltage sensor and the pore domain) is statistically significant in predicting a negative prognosis. It is well known that *KCNQ2* gene share a common design of four α subunits, each α subunit contains six transmembrane segments, with cytoplasmic N-terminal (short) and C-terminal (long) regions, S1–S4 forming the voltage sensor and S5–S6 forming the pore-lining domain^[24–25]. S4 plays as the main sensor for depolarization^[24–26]. The pore loop (H5) between S5 and S6 is a highly conserved pore region, and functions as K⁺ permeability and selectivity filter^[24–26]. Variants associated with epileptic encephalopathy and located in the pore region or S4 segment produce dominant-negative effects and reduce current density by 50–70%^[27–28].

In this study, long-term outcome was usually worse when the variant location was in voltage sensor and the pore domain even early VEEG score was same. For example, patient 26 with a variant in S4 segment with early VEEG score 1, had a mild impairment development, while other patients with early VEEG score 1 usually had a normal development; patient 27 with a variant in S4 segment with early VEEG score 2 had a moderate or severe impairment development, while other patients with early VEEG score 2 usually had a normal or mild impairment development. Correspondingly, the long-term outcome was relatively mild when variant location was not in voltage sensor and the pore domain. For example, patient 42 with a variant in S2-S3 linker with early VEEG score 3 had a normal development, while other patients with early VEEG score 3 usually had a moderate or severe impairment development.

It has been found that pathogenic variants in *BFNS1* occur throughout the gene, including exon and whole-gene deletions; pathogenic variants in *EIEE7* cluster in four functionally important protein domains: voltage sensor, the pore, C-terminus proximal region (important for modulation by second messengers), and calmodulin-binding B helix region^{[11][29]}. But two recent studies are slightly different; one showed “severe or epileptic encephalopathy (EE)” missense variants cluster at S4, the pore loop that contains the selectivity filter, S6, helix B, and the helix B-C linker^[21]; the other reported that the EE missense variants cluster at the pore domain, S6, and pre-helix A^[20]. With in-depth study of the *KCNQ2* gene and protein function, the variant location, including calmodulin binding region and the region for modulation, may have an impact on our model.

Two recent studies on variant location of severe development or EE were missense variants in *KCNQ2* gene^[20–21]. In fact, regardless of the previous reports or our study, there are some non-missense variants in the patients with encephalopathy. It is interested that a case harbors a de novo deletion (c.913_915delTTC p.Phe305del) located in S6 segment developed a spastic-dystonic tetraplegia with severe dysphagia^[30]. We speculate non-missense variants in voltage sensor, the pore domain, etc, should also be more likely to cause severe impairment development.

According to the prognosis, we found that there were few patients with *KCNQ2*-related disorder whose outcome was between benign and encephalopathy. The intellectual development of these patients was

slightly impaired. The early VEEG of these patients showed multifocal epileptiform activity with normal sleep-wake cycles. The number of abnormal discharges was more than that of the patients with normal outcomes, but less than encephalopathy ones. This intermediate type between benign and encephalopathy has also been reported in other researches^[11–12, 31]. Some studies defined this group as benign, some put them into encephalopathy group. In our study, we believe it should be defined as a new independent group.

Same variant in *KCNQ2* can cause different phenotypes varying from mild forms to severe forms. Similarly, in our study, VEEG with the same score could not determine whether it had the same prognosis. Both variant location and VEEG are related to the prognosis, so we combine the two factors to predict the prognosis. *KCNQ2*-related disorder is a rare disease, a cohort of 52 cases is a large sample size for a single-center study. Besides, it still needs to be supported by more samples from multi-center or long-term follow-up data.

Conclusion

Two combined clinical characteristics, VEEG and variant location, provide clinicians a method for assessing prognosis of *KCNQ2*-related disorder. A neonate with a *KCNQ2* variant location in voltage sensor or the pore domain, worse VEEG background, usually had a poor prognosis.

List Of Abbreviations

BFNS1

benign familial neonatal seizures 1; EIEE7 = early infantile epileptic encephalopathy 7; VEEG = video-electro-encephalography; AEDs = anti-epileptic drugs; FSIQ = full scale IQ; SD = standard deviation; IQR = interquartile range; EE = epileptic encephalopathy.

Declarations

Ethics approval and consent to participate: All samples used in this study were collected with appropriate informed consent and approval of the ethics committees of Children's Hospital of Fudan University (approval number 2019-16). The methods used in this study were carried out in accordance with the approved guidelines.

Consent for publication: Not applicable.

Availability of data and material: All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: XY, DYL, ZYF and CGQ, contributed to the conception, design, data acquisition, data analysis, data interpretation, and drafting of the work; XY, DYA, CX, DXR, WXH, WBB, ZYF and CGQ contributed to the acquisition and analysis of data; XY, DYL, ZYF and CGQ, contributed to drafting the text and preparing the figures.

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Figures

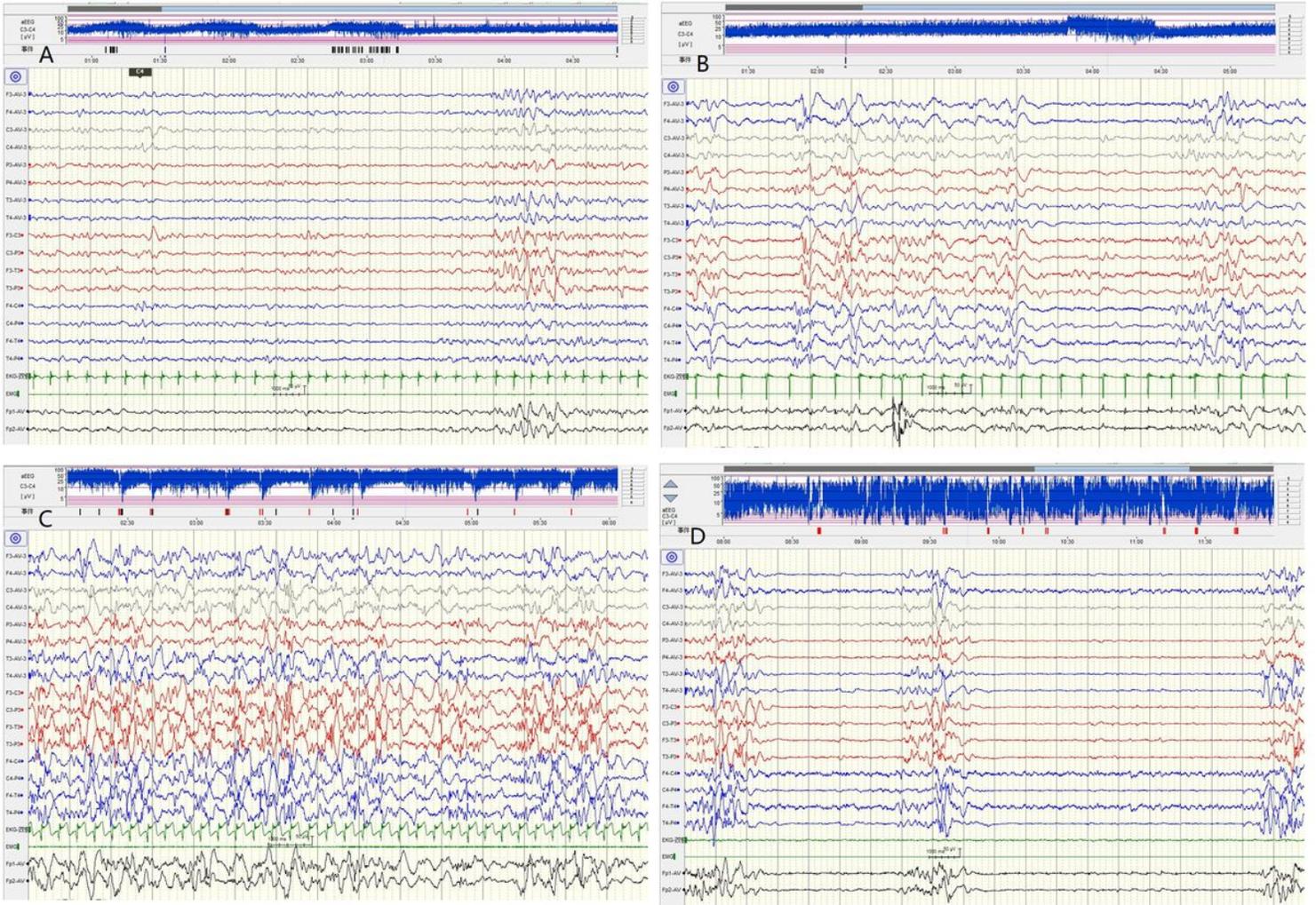


Figure 1

A: Patient 8, mildly abnormal: mild multifocal sharp waves. B: Patient 5, moderately abnormal: multifocal sharp waves, with sleep cycle. C: Patient 2, moderately abnormal: multifocal sharp waves, without sleep cycle. D: Patient 29, markedly abnormal: burst-suppression pattern.

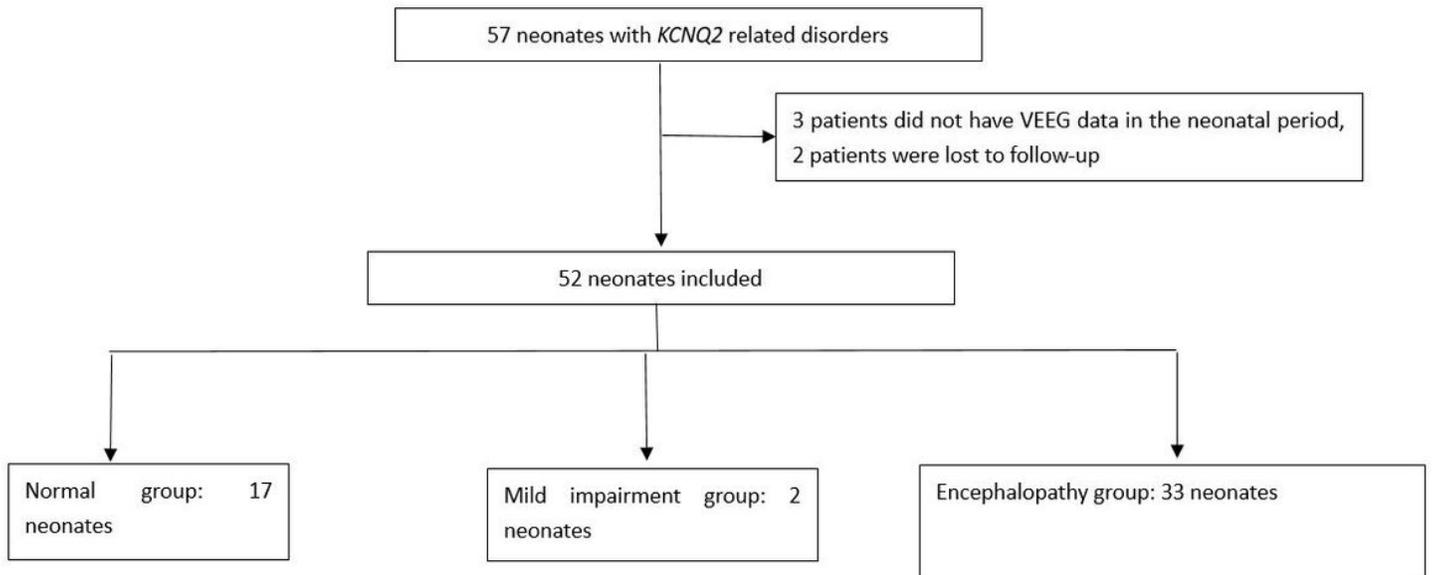


Figure 2

Study profile.

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