Epilepsy & Behavior 142 (2023) 109153

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clinical characteristics of 80 subjects with KCNQ2-related encephalopathy: Results from a family-driven survey

A. Cossu [a,b], T. Lo Barco [a,b], J. Proietti [a,b], B. Dalla Bernardina [b], G. Cantalupo [a,b], L. Ghobert [a,b], I. Brambilla [b,c,d,e], E. Giarola [b,c,d], A. Costa [e], T. De Benito [f], S. Bethge [g], S. Cardot [h], Iga Montwill [i], E. Remonato [c,e], S. Gramaglia [e], F. Darra [a,b,*]

[a] Child Neuropsychiatry Unit, Department of Surgery, Dentistry, Paediatrics and Gynecology, University of Verona, Full Member of European Reference Network EpiCARE, Verona, Italy
[b] Research Center for Pediatric Epilepsies (CREP) - Department of Surgery, Dentistry, Paediatrics and Gynecology, University of Verona, Italy
[c] Alleanza Epilessie Rare e Complesse, Italy
[d] Dravet Italia Onlus, Epag ERN EpiCare, Verona, Italy
[e] European KCNQ2 Association Odv, Italy
[f] Asociación KCNQ2 España, Spain
[g] KCNQ2 e.V. Germany, Germany
[h] KCNQ2 France Développement, France
[i] KCNQ2 Poland Group, Poland

ARTICLE INFO

Article history:
Received 26 September 2022
Revised 17 February 2023
Accepted 19 February 2023

Keywords:
KCNQ2
Encephalopathy
Outcome
Caregiver
Severity
Phenotype
Epilepsy
Neonatal seizures

ABSTRACT

Variants of KCNQ2 are associated with a wide spectrum of disorders, ranging from Self-limiting Neonatal Epilepsy (SelNE) to Early Onset Developmental and Epileptic Encephalopathy (KCNQ2-DEE). Comorbidities associated with this end of the spectrum have been seldomly described and their impact on the life of patients and their families is yet to be investigated.

Collaborating with caregivers from different European family associations, we have developed a questionnaire aimed at investigating the onset and frequency of epileptic seizures, anti-seizure medications (ASM), hospitalizations, stages of development, and comorbidities.

Responses from 80 patients, 40 males, from 14 countries have been collected. Median age 7.6 years (4 months – 43.6 years). Of 76 epileptic patients (93.6%), 55.3% were seizure-free with a mean age at last seizure of 26.7 months. Among patients with active epilepsy, those older have a lower frequency of seizures ($p > 0.05$). We were able to identify three different clusters of varying severity (Mild, Severe, Profound), based on neurodevelopmental features and symptoms, excluding epilepsy. Patients in a higher severity cluster had a higher mean number of comorbidities, which had a higher impact on families. Notably, patients in different clusters presented different epilepsy onset and courses.

This study constitutes the most extensive data collection of patients with KCNQ2-DEE, with a focus on comorbidities in a wide age group. The participation of caregivers helps to define the impact of the disease on the lives of patients and families and can help identify new primary and secondary outcomes beyond seizures in future studies.

1. Introduction

The KCNQ2 gene encodes for Kv7.2 voltage-gated potassium channel subunits responsible for the M-current, widely expressed in the central nervous system. Both gain-of-function and loss-of-function mutations in KCNQ2 are associated with a wide spectrum of disorders, ranging from Self-limiting Neonatal Epilepsy (SelNE) to Developmental and Epileptic Encephalopathies (KCNQ2-DEE), with onset in the neonatal or early infantile period [1]. The electro-clinical phenotype at the severe ends of the spectrum has been widely described in recent years [2], however, the incidence of disorders beyond epilepsy has seldom been investigated and reported [3].

In the last 2 years, the assessment of the quality of life and the impact on the daily life of genetic encephalopathies have been an expanding research field [4–6]. The determination of the involvement beyond the neurological system is needed to assess the overall health of this class of patients and as a tool to better investigate quality-of-life and daily issues. In this study, the aim

* Corresponding author at: Piazzale Stefani 1, 37126 Verona, Italy.
E-mail address: Francesca.darra@univr.it (F. Darra).

https://doi.org/10.1016/j.yebeh.2023.109153
1525-5050/

is to investigate the characteristics of this involvement in KCNQ2-DEE with the participation of caregivers in the study design.

2. Methods

This questionnaire was written with the guidance of caregivers from 4 family associations for KCNQ2-related encephalopathies (European KCNQ2 Association Odv, Association KCNQ2 España, KCNQ2 Einblick Beratung Netzwerk E.V., KCNQ2 France Mila) and with the collaboration of the Alliance of Rare and Complex Epilepsies.

The survey was developed using G Suite™ tools (Google, CA, USA) and shared through the four association networks. The survey was available in Italian from 20th December 2020 to 10th January 2021. The questions were then translated into English, French, German, and Spanish and made available in all five languages from 10th February to 30th March 2021. A sixth version in Polish was translated and made available online from the 15th of March to the 15th of June 2021. One caregiver per patient was allowed to complete the survey, anonymously.

This questionnaire explores the following issues, derived from literature [7–10] and defined with caregivers' cooperation:

- Age and auxological data;
- Pregnancy and delivery;
- Epilepsy onset, seizure type, frequency, and treatment (continuous or rescue medication);
- Neuroradiological findings, EEG, and age at genetic diagnosis;
- Need and cause for urgent care and other hospitalizations;
- Covid-19 impact on routine care;
- Comorbidities classified as Gastrointestinal (GI), Orthopaedic, Visual, Urinary,
- Dermatological, and Endrocrinological issues;
- Free text description of comorbidity for every issue category;
- Neurological symptoms;
- Developmental milestones;
- Rehabilitation and school attendance;
- Monthly cost of care and impact on the main caregiver.

2.1. Statistical analysis

Statistical analysis was made using SPSS Statistics Version 25.0 (IBM Corp, NY, USA). Since the number of responders varied in each question, frequencies are reported as percentages, and the number of answers over the total number of responders is in parentheses. Taking into consideration the varying sample size, all statistical analyses were carried out using non-parametrical methods and normal distribution was not confirmed. Continuous variables are reported as means and ranges in parentheses. Correlations between category variables were carried out using chi-square (X^2). Relationships between continuous and category variables were carried out using non-parametric analysis, U Mann-Whitney, and Kruskal-Wallis ANOVA depending on the number of subgroups (two or more than two respectively). Correlations were deemed significant with a $p < 0.05$.

Free text answers were transformed into category variables by a physician with expertise in the holistic care of DEE patients (TLB).

The reported results of the Cluster analysis were obtained via a Two-step Cluster analysis with the following variables as input, without specifying the number of desired clusters:

- Motor skills in patients older than 2 years old, categorical ordinal variable.
- Feeding abilities in patients older than 2 years old, categorical ordinal variable.
- Muscle tone in patients older than 2 years old, categorical ordinal variable.
- Language skills in patients older than 2 years old, categorical ordinal variable.
- The presence of autism and motor stereotypies in patients older than 2 years old, both categorical dichotomic variables.

These variables were chosen to represent the neurodevelopmental picture of these patients regardless of epileptic phenotype, which was later described per different severity clusters. Nine patients aged below two years old were excluded to guarantee comparison between patients with similar expected developmental milestones.

3. Results

Demographical data are reported in Table 1. Moreover, 4 groups of comparable size were identified; 24% were younger than 3 years old, 25% were between 3 and 6 years old, 27% were between 6 and 9 years old, and 24% were older than 9 years old.

We received answers from 14 countries on 3 continents, however, 92% of answers were collected from European families, in particular, 22% of all 80 families are from Italy.

3.1. Auxological data

The weight percentile (W%) ranged from 1st to 98th (mean 31.7), the height percentile (H%) ranged from 1st to 99th (mean 37.7) and the head circumference percentile (HC%) ranged from 1st to 99.7th (mean 48.3). Twenty -two percent of participants had an HC% below the 3rd percentile, 28% had a height below the 3rd percentile and 31% weighed below the 3rd percentile.

3.2. Perinatal information

The course of pregnancy was described as normal in 71% (57/80) of cases and pathological in 29% (23/80).

Fifty-five percent (44/80) of participants needed to be admitted to a NICU at birth; among them 73% (32/44) presented seizures, 18% (8/44) had respiratory complications, 4% (2/44) presented hypoglycemia, while 4% (2/44) did not specify.

3.3. Epilepsy

Among all participants, 94% (75/80) presented a form of epilepsy. Among epileptic patients, the age at onset was on the first day of life in 55% (24% within the first 10 hours), 23% on the second day of life, 4% on the third day, 8% between the 4th and 10th, and 9% after the 10th day. In 85% of cases with epilepsy, onset was recognized in the first 10 days of life, and 9% presented with seizures later than the 10th day of life.

Furthermore, 76 families answered regarding the reference to a burst-suppression pattern in the first EEG report. Thirty-five percent (27) answered affirmatively, while 41% did not know, and 24% answered negatively.

All patients received, for a variable time, an antiseizure treatment. Fifty-one percent of all responders (41/80), aged between 5 months and 32 years, are seizure free at the time of survey com-

Table 1
Reporting demographical data of the population.

Sex (n = 80)	Male (39; 49%); Female (41; 51%)
Age (median; min–max)	7.6 years (4 months-43.6 years)

pletion, with an age at last seizure occurrence between 2 months and 10 years. Eleven subjects are untreated at survey completion, aged between 5 months and 29 years. Among them, the mean age at the last seizure was 26.5 months and the median age was 8 months (minimum 1, maximum 144). Among the 49% (39/80) of patients that still presented seizures, 27% reported rare episodes and 17% reported daily seizures. Seizure frequency was related to the age group, with patients younger than six reporting daily seizures more frequently compared to patients older than 6 years old ($p < 0.05$ X^2, V Cramer: 0.424). In particular, 3/6 patients under 3 years of age and 5/6 patients between 3 and 6 years old, who had seizures, reported a daily frequency. Adding to this, 64 participants answered regarding seizure frequency during their life-time. Sixty-nine percent of them (44/64) reported daily episodes, 8% (5/64) more than weekly, 8% (5/64) between 2 and 4 per month, and 16% (10/64) as rare.

3.3.1. Seizure types

Sixty-five caregivers responded regarding seizure types, and 60% (39/65) listed the presence of more than one seizure type. Among all 80 participants, 51% (41/80) mentioned the recurrence of epileptic spasms, 36 patients answered on the age at spasms onset, 36% (13/36) said they appeared in the first month of life; the mean age at onset was 5.17 months (range 0–36 months).

3.3.2. Epilepsy treatment

Sixty-three participants responded regarding the use of emergency drugs in the treatment of seizures. 56% (35/63) never used emergency drugs, while 36% (23/63) used them rarely. 3% (2/63) used emergency drugs 1 or 2 times per month, while 5% (3/63) used them 3 or 4 times. There was no correlation between age and the need for emergency treatment of seizures. However, a higher seizure frequency correlated with a more frequent need for emergency treatment ($p < 0.01$). This correlation was explored in the different age groups, showing a significance in patients older than 9 years old ($p < 0.05$).

Among all 80 patients, 21% (17/80) did not take any ASM, while 41% (33/80) took one, and 38% (30/80) took 2 or more. Among those treated with ASM, 63% (40/63) took Sodium Channel Blockers (SCBs), as the single ASM in 18 cases.

Twelve percent (10/80) of all responders reported to be following a ketogenic diet as part of anti-seizure treatment in their life-time, and 10% (8/80) were following it at the time of survey completion.

Regarding the 6% (5/80) of patients who did not present epilepsy, the mean age was 6.3 years old (range 2–11 years old), and all 5 had genetic confirmation of a *de novo* variant in KCNQ2. In 2/5 cases the pregnancy was reported as pathological, however, none of them needed NICU admission at birth. The neurodevelopmental picture at the time of survey completion was characterized by the inability to walk in 2/5 (one patient needing head-up support), and the need for supervision during feeding in 4/5 patients (three needing supervision most times). From the language point of view, two patients can utter words, one was non-communicative, and two could produce sounds/syllables.

The need for hospitalizations and the impact of comorbidities are reported in Fig. 1 and Table 2 respectively. The latter in particular report a mean number of comorbidities of 2.4 (range 0–5) with the most frequent being visual issues in 57% (46/80) followed by gastrointestinal issues in 46% (37/80) (with constipation in almost one-third of patients) and orthopedic issues in 46% (37/80).

3.4. COVID-19 impact

Forty -seven percent (38/80) reported a reduction in check-up visits related to the pandemic. 60 caregivers responded regarding the use of telemedicine, with 57% (34/60) reporting telemedicine as a tool for continued healthcare even without having a check-up reduction due to the pandemic. Similarly, 58% (46/80) of responders report a reduction in rehabilitation visits due to COVID-19.

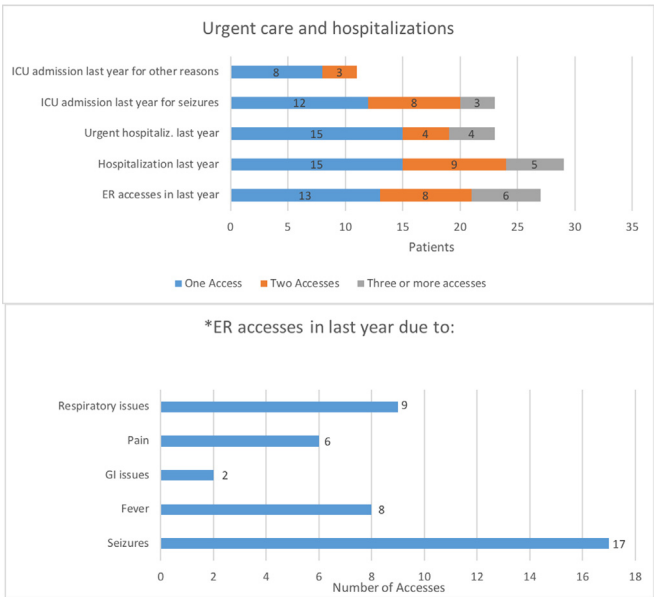

Fig. 1. Reports the numbers of patients who needed Emergency Room (ER) accesses in the last year prior to the survey and the reason for ER access; the number of hospitalizations, elective (29/80, 36% with at least one admission) and urgent (23/79, 29% with at least one admission), and the number of Intensive Care Unit (ICU) admissions (23/79, 26% with at least one admission), in the last year prior to survey. Patients that accessed the ER at least once in the last year were 34% 27/80, the most frequent reason were seizures (21% 17/80), followed by respiratory issues and fever.

Table 2
Reports the number and subtype of comorbidity reported by caregivers. 83.7% of all responders complained of at least one comorbidity and the mean number of comorbidities per patient was 2.39. The most reported subtype was Visual Issues, followed by Gastrointestinal and Orthopaedic issues.

Comorbidities			
Number per patient (mean)	2,39		
Gastrointestinal Issues	**46,30%**	**Urinary tract Issues**	**16,30%**
Reflux	15%	Recurrent cystitis	5%
Poor Eating	1,30%	Urinary retention	8,80%
Constipation	31,30%	Other	2,50%
Diarrhea	3,80%		
Aspecific Abdominal Pain	3,80%	**Dermatological Issues**	**18,80%**
Other	2,50%	Eczema	6,30%
		Dermatitis	5%
Orthopedic Issues	**46,30%**	Other	8,80%
Hip subluxations	11,30%		
Scoliosis	11,30%	**Endocrinological Issues**	**5%**
Deformations (Clubfoot)	12,50%		
Flatfoot	10%	**Visual Issues**	**57,50%**
		Strabismus	32,50%
Respiratory Issues	**8,80%**	Low Vision	23,80%
Apnoea	5%	Nystagmus	2,50%
Other	3,80%	Other	22,50%

3.5. Neuropsychological development

Caregivers were given a set of questions regarding adaptative skills, motor skills, language, and the presence of autism-like behavior. Among all 80 responders, 45% (36/80) carried out at least one developmental assessment. Seventy eighty percent (28/36)

had the last neurodevelopment assessment before the age of 6, with the 14% (5/36) before the age of 2.

Autism was diagnosed in 14% (11/80) of cases. Caregivers described the social relationships of the child with peers as poor in 54% (43/80) of responses and fair or good in 44% (35/80).

3.5.1. Feeding

In the feeding domain, most responders reported feeding by mouth, in particular, 94% (75/80) were fed by mouth, with 44% (35/80) following a free diet and 49% (39/80) consuming primarily semi-solid foods. One individual was fed by a nasogastric tube and four underwent percutaneous endoscopic gastrostomy (PEG).

Among patients that were fed by mouth and over 2 years old, 5% (4/75) were independent in feeding, among the other responders 45% (34/75) were dependent on caregivers for help and supervision, while 29% (22/75) needed help most times, and 9% (7/75) needed help only sometimes.

3.5.2. Motor skills

Of the 9 responders with children under 2 years old, 4 (44%) stated the child had motor skills compared to their peers, while 1 (11%) reported skills slightly delayed and 4 (44%) moderately to severely delayed.

Among individuals over 2 years old, 25% (18/71) said they could not keep their heads up and 15% (11/71) could with support. Five percent (4/71) could sit on their own, but could not stand up and walk independently, while 15% (11/71) could stand up and walk with aid. Lastly, 38% (27/71) mentioned the person could walk independently. Out of these 27 patients, 15 could run, jump, and climb stairs, 5 could only run and jump, 2 could run, and 5 could only walk.

Sixty caregivers reported regarding sphincter control, 75% (45/60) of all responders stated the person was unable to keep themselves clean, while 3% (2/60) could alert when needed, and 21% (13/60) could retain control day and night.

3.5.3. Motor symptoms

Furthermore, in the motor domain, 49% (39/80) mentioned generalized hypotonia, while 16% (13/80) had hypertonia, with 14% (11/80) listing spasticity in particular. Four cases (5%) needed treatment for hypertonia/dystonia.

When asked about posture, 37% (30/80) of caregivers reported a wide-open mouth (with or without tongue protrusion), 27% (22/80) anomalous position of the head and trunk, 11% (9/80) an unusual, fixed position of one or more limbs, 12% (10/80) limbs in a rigidly twisted position. Sixty-five percent (52/80) of responders mentioned the presence of motor stereotypies.

3.5.4. Language

Regarding language, families of persons older than 2 years old (71 patients), declared the absence of language in 61% (43/71) of cases. Among the others, 7% (5/71) spoke adequately for their age. Out of the remaining 32% of responders, 14% (10/71) reported speaking a few words, 5% (4/71) produced syllables, 10% (7/71) produced sounds and 3% (2/71) used gestures.

3.6. Sleep

Regarding the presence of sleep disorders and sleep disturbances, 67% (54/80) of caregivers reported sleep problems, with 42% (34/80) indicating difficulty falling asleep and 45% (36/80) difficulty staying asleep. On the other hand, only 11% (9/80) of responses mentioned excessive daytime sleepiness. Furthermore, 24% (19/80) of families used a specific medication or supplement to facilitate falling asleep.

Only rarely caregivers stated a clear relationship between sleep and the recurrence of seizures, 11% (9/80) of families reported seizures in the transition between wake and sleep, 4% (3/80) noted being wakened in the night by seizures, and 7% (6/80) describe episodes early in the morning.

3.7. Daily activities and rehabilitation

3.7.1. School or other activity

Questions were asked on whether or not patients attended any kind of structured daily activity and caregivers on whether children attended school in the different grades, and whether adults attended institutes or special schools.

Among responders 19 total families (24%) reported the children attended a nursery, 16 families said the child or adolescent attended a primary school, and 3 caregivers said their family member attended high school. Furthermore, 11 families (14%) listed their attendance at a day-time center. Eleven persons (13%) attended an institute. Fifteen families (19%) declared attendance at a special school.

Out of all 80 families, 40% (32/80) undertook other daily activities, such as sports, art, and music therapy or equine-assisted therapy.

3.7.2. Rehabilitation

Among all 80 responders, 39% (31/80) attended a psychomotricity program, and 58% (47/80) a physiotherapy or kinesitherapy program, evenly distributed among all age groups.

Ten undertook occupational therapy or cognitive rehabilitation programs, 7 attended an alternative communication program and 58 (48/80) a speech therapy program. Furthermore, 2 undertook a respiratory physiotherapy program.

3.7.3. Cost

Seventy-eight caregivers answered regarding the cost and coverage of rehabilitation programs. In 49% (38/78) of responders, rehabilitation is mostly performed at the direct expense of families. In particular, 25% (19/78) of families directly take care of the cost for all hours of rehabilitation, while in 14,3% the family is charged for almost all. In the other half of cases, the cost is mostly charged to the national healthcare system; in this group, 20% (16/78) of families reported participating in less than half of all hours of rehabilitation.

In regards to the amount charged for rehabilitation, 49% of families (38/78) declared paying between 0 and 200€ monthly, 21% (15/71) between 200 and 500€, 24% (17/71) between 500 and 1000€, while only 11% (8/71) more than 1000€.

Patients of families that spent more than 500€/month on rehabilitation presented a higher number of comorbidities ($p < 0.005$, Mann-Whitney).

3.8. Caregiver

In 10% (8/80) of cases, caregivers benefited from the help of hired babysitters, 15% (12/80) received help from grandparents or other family members and 4% (3/80) had home assistance from specialized personnel (nurses or social workers). In 64% (51/80) of all participating families, one parent had to give up their job or reduce their work hours to take care of their child. In 30% (24/80) of families, in fact, one of the parents did not work, in order to be independent in the care of the child.

From the caregivers' perspective, the issues that impacted most the well-being of their child were developmental delay in 14% (11/80), followed by movement disorder in 11% (9/80) of cases, seizures in 7% (6/80) of cases, muscle tone in 6% (5/80) of cases and language in 5% (4/80). Other cited issues were autism, pain, gas-

trointestinal issues, respiratory problems, vision, sleep issues, feeding issues, and osteoarticular problems.

Further investigation is concerned if there were any differences in these variables among patients answering from the five countries who counted the most participants to the survey: Italy (18), Spain (14), Poland (14), France (11), and Germany (9). Notably, the mean age of patients from these countries was different, with a lower mean age in France and Poland (6.7 and 3.8 years old, respectively); furthermore, there were no French patients under 3 years old, and a higher portion of this group was of Polish origin (8/13).

The different attendance of rehabilitation programs in the different countries is reported in Table 3. The most frequently attended programs were physiotherapy and speech therapy, at the sample level, and in all single countries except France, where psychomotricity was the most attended. The discrepancies in the attendance of the different programs could be explained by the different age group prevalence in different countries, reflected in the different mean ages in these subgroups.

Regarding costs, families from Germany reported (8/9) that rehabilitation cost is totally at the expense of the NHS. In France and Italy, the cost is reported at the expense of the NHS (wholly or more than half of the hours) in around half of the cases (55% (6/11) and 50% (9/18) respectively). Families from Spain reported paying for all or most of the rehabilitation hours in 86% (12/14) of cases. This difference is partially resembled in the reported monthly cost of rehabilitation, with families from Germany paying less than 200€/month, and families from Spain paying more than 500€ in 50% (7/14) of cases and more than 1000€ in 14% (2/14). Families from Italy and France reported different amounts, with families from Italy spending more than 500€ in 39% (7/18) versus 27% (3/11) in France (no French families reported spending more than 1000€, versus four in Italy).

The change in habits of caregivers is also different among countries. Most caregivers across all five countries have changed their workload in order to spend more time with their child (61% (11/18) in Italy, 71% (10/14) in Spain, 67% (6/9) in Germany, 82% (9/11) in France, and 64% (9/14) in Poland). However, in Italy, a higher percentage of caregivers gave up their job in order to assist the child in place of other staff (44% (8/18) versus 28% (4/14) in Spain, 29% (4/14) in Poland, 22% (2/9) in Germany, and none in France).

3.9. Magnetic resonance imaging

Seventy-five families answered regarding the execution of an MRI scan and its findings. Among those, 96% (72/75) carried out at least one MRI scan, and 63% (47/75) of individuals completed more than one. The average age at the time of the first scan was 5.87 months old, with a median of 1 month old.

The MRI found an abnormality in 43% (32/75) of cases. Among these findings, the families listed: hypomyelination in 37% (12/32), white matter abnormalities in 12% (4/32), cortical atrophy in 9% (3/32), malformation of cortical development in 6% (2/32), thin corpus callosum in 28% (9/32), and other nonspecific abnormalities in 50% (16/32) of patients. Notably, one family mentioned the presence of brain oedema, and another individual presented with a stroke.

3.10. Genetics

All 80 families participating in the survey received a genetic diagnosis of KCNQ2-related disorder. One patient carried a partial deletion of KCNQ2. In 9% (7/80) cases, the investigation was not extended to the parents; among the other 73 families, 88% (64/73) carried a *de novo* variant, 4 were waiting on further results, and 5 were inherited mutations. Among these 5 families, 1 patient was younger than two-years-old, 1 patient was classified in the severe phenotype cluster, and 3 patients were classified in the milder phenotype cluster. Interestingly, the 3 in the milder cluster had one of their parents suffering from seizures during infancy. In this population, the prevalence of asymptomatic carrier parents is in line with the literature [12] as between 5% and 28%.

Regarding the age at diagnosis, the mean age was 1.12 months old with a median of 1 month and a 75th percentile at 2 months.

3.11. Cluster analysis

A cluster analysis was taken into account regarding motor skills, feeding abilities, muscle tone, language, the presence of autism, and motor stereotypies. These variables were investigated in the 71 patients older than 2 years, in order to obtain a more homogeneous developmental phenotype with comparable milestones in motor and language development.

The resulting clusters were identified as follows:

1. Milder phenotype (n = 30, 42%) characterized by the ability to walk, feeding by mouth with a diet of varied consistency, normal muscle tone or mild hypotonia, and productive language. Greater incidence of diagnosis of autism. Lower incidence of epilepsy (see Table 4).
1. Severe phenotype (n = 19, 27%): the ability to sit and stand independently but not to walk, feeding with a diet of semi-solid consistency, spastic muscular hypertonia, and language characterized by sounds or syllables. Minor incidence of autism diagnosis. Epilepsy in nearly all cases.
2. Profound phenotype (n = 22, 31%) characterized by the inability in keeping one's head up, feeding with a semi-solid diet or by PEG, and varying muscle tone with hypotonus and hypertonus. The totality of patients were non-verbal. None of them received a diagnosis of autism, all patients were epileptic.

These three groups differed for auxological data, with patients in the Profound phenotype group presenting with a significantly lower W%, H%, and HC% ($p < 0.05$). Furthermore, patients in the Milder phenotype were less frequently treated with ASMs, and patients in the Profound phenotype group more frequently presented with hypomyelination or myelination delay at the MRI (9/12, $p < 0.05$), and with epileptic spams (17/37, $p < 0.05$).

Patients in the Severe and Profound phenotype presented more frequent sleep problems (14/19 and 19/22 respectively, $p < 0.05$).

The mean age was comparable between groups (Milder 9.1 years old (range 2–43 years), Severe 8.6 years old (range 2–

Table 3
Shows the distribution of rehabilitation program attendance, over the whole cohort and divided by the five most represented countries.

	Overall	Italy	Spain	Poland	France	Germany
Psychomotricity	38.8%	44.4%	35.7%	35.7%	81.8%%	–
Speech Therapy	58%	55.6%	85.7%	42.9%	27.3%	77.8%
Physiotherapy	58%	66.7%	71.4%	78.6%	9%	66.7%
Occupational Therapy	12%	–	42.9%	–	18.2%	–

Table 4
Shows the frequency of variables describing the epileptic phenotype in the whole population and the different clusters.

Epilepsy phenotype population and by cluster		Overall (n = 80/100%)	Milder phenotype (n = 30/37,5%)	Severe phenotype (n = 19/23,7%)	Profound phenotype (n = 22/27,5%)	Under 2 years old (n = 9/11,5%)
Presence of Epilepsy		75 (93,7%)	26	18	22	8
Age at seizure onset	Within 10 hours	18 (24%)	2	5	10	1
	10–24 hours	23 (31,5%)	10	4	7	2
	24–48 hours	17 (23%)	8	4	3	2
	48–72 hours	3 (3,7%)	–	1	1	1
	Between 3rd and 10th day	6 (8%)	2	2	–	2
	After the 10th day	7 (8.8%)	4	1	1	1
Current seizure frequency	Seizure-free	41 (51,2%)	18	9	9	5
	Rare	20 (25%)	6	6	6	2
	2–4 months	2 (2%)	–	2	–	–
	Multiple per week	3 (3,7%)	1	–	2	–
	Daily	9 (11,5%)	1	1	5	2
	If seizure-free mean age at last seizure (months)	26.5 (1–144)	20.9 (1–125)	49 (2–144)	29.8 (3–108)	4 (1–11)
Seizure frequency in the past	< 2 a month	10 (12,5%)	5	1	4	–
	2–4 a month	5 (6,2%)	1	2	2	–
	Multiple per week	5 (6,2%)	3	1	–	1
	Daily	44 (55%)	11	12	15	3
Recurrence of infantile spasms		41 (51,2%)	11	9	17	4
Report of Burst-Suppression at first EEG		27 (33,7%)	3	6	15	3

29 years), Profound 7.5 years old (range 2–32 years)), therefore the clinical differences are not explained by a progressive deterioration with age.

Regarding onset, the patients in the Profound and Severe phenotype needed NICU admission in higher numbers, compared to the Milder phenotype.

Regarding hospitalization and comorbidities, patients in the Severe phenotype needed emergency health care significantly more frequently than the other groups (2.05 mean accesses in the last year, $p < 0.001$). Patients in the Profound phenotype group, presented with a higher mean number of comorbidities (3.4, $p < 0.001$), in particular, caregivers complained more frequently of visual inattention/low vision ($p < 0,05$).

The difference in the epileptic phenotype in the three groups is reported in Table 4.

Interestingly, we found a difference within our sample in the reported age at seizure onset, with a higher frequency of patients presenting seizures in the first 10 hours of life in the profound phenotype cluster, while the high percentage of onset in the first day of life was retained across all clusters. Also, regarding epilepsy onset, a majority of patients with a reported burst-suppression pattern at first EEG belong to the Profound phenotype cluster. Furthermore, patients who presented with epileptic spasms were more frequently assigned to that same cluster.

Regarding seizure frequency, a higher portion of patients in the Milder cluster was reported seizure-free, compared to the other two groups. Among the patients who still presented seizures, patients in the Profound phenotype reported daily seizures more frequently, compared to the other clusters. Among the seizure-free patients, the mean age at the last seizure was higher in patients in the Severe cluster. Furthermore, the Severe and Profound clusters do not include any patients with epilepsy limited to neonatal age.

4. Discussion

Findings describe a cohort of KCNQ2-DEE patients, as reported by their caregivers. In our cohort epilepsy is a predominant feature, being present in 94% of responders during their lifetime. However, a majority, 55%, reported being seizure-free at the time of survey completion, to which one could arguably add, the group of patients who reported rare seizures, grouping patients with "inactive epilepsy". In contrast, however, of the 41 seizure-free patients, only 11 were untreated, which could suggest the clinical necessity of continued treatment, despite the drop in seizure frequency. The reason for continuous ASM treatment, especially in patients older than 13 years old, remains unclear. Moreover, some patients could have persisting epileptiform abnormalities on the EEG, which could further account for the non-discontinuation of ASMs. Furthermore, among seizure-free patients, the distribution of the age at the last seizure shows that the most frequent age of florid epilepsy is the first 2 years of life (median 8 months – average 26.5 months, standard deviation 37.6 months), with a successive attenuation or cessation of seizures. This is reflected in the correlation between age and seizure frequency, with older patients reporting less frequent seizures compared to patients younger than 6 years old.

Regarding the neurodevelopmental phenotypes, this report identifies three groups of varying severity, via a cluster analysis based on reported neurodevelopmental symptoms, excluding epilepsy. Interestingly, the epileptic phenotype was different among these patients. In particular, patients with a Profound phenotype represented the majority of patients with seizure onset in the first 10 hours of life and presented more frequently with burst-suppression patterns. This class of patients also presented more frequent epileptic spasms compared to the other groups. Regarding seizure frequency at the time of survey completion, however, no difference was found among the three groups in patients with ongoing epilepsy. As already suggested by Berg and collaborators [3], these findings strengthen the hypothesis that seizure frequency is not the only factor determining the neurodevelopmental phenotype in this class of patients. The impact of seizures and active epilepsy, however, should not be overlooked as a determining factor in the quality-of-life of the patients and their families [4]. Furthermore, certain times of epilepsy onset and certain epilepsy features, seem to be associated with different phenotypical outcomes, possibly linked to genotype. A limitation of this study is, in fact, the lack of investigation of possible correlations between phenotype and the patients' variants and their functional effects. This could further help the grouping in more homogenous phenotypes, between gain-of-function and loss-of-function carrying patients. The methodology applied, in addition, has inherent limits, in particular the gathering of clinical data from caregivers, which could infringe on its accuracy. However, many of the reported findings are in line with what has already been reported in the literature regarding KCNQ2-DEE [11,12].

The methodology applied takes into heavy account the input from caregivers, not only in the gathering of data but also in the definition of variables and wording of the questions. This is, in our opinion, a novel and vital part of our study, and strengthens the findings regarding comorbidities, clinical and rehabilitation costs, and the impact of disease on a caregiver's life. This class of patients has, in fact, a high need for care, with a high frequency of inpatient admission, both elective and urgent or intensive. Our results report a high number of visual issues, in particular low vision/visual inattention, as previously reported [3]. We also confirm the high prevalence of gastrointestinal issues, albeit not as high as previously reported [13]. We also report a high number of orthopedic issues, like hip subluxations and other deformities.

Findings show that a Severe or Profound phenotype have a higher impact in terms of monthly rehabilitation costs, needing more frequently more than 500€/month on rehabilitation programs. Furthermore, patients with a Profound phenotype have a higher number of comorbidities, and patients with a Severe phenotype needed urgent care more frequently than other groups. The country of origin also plays a role in the cost of rehabilitation undertaken by families and the impact of the disease on the caregivers' careers and extended family.

5. Conclusions

The findings from a worldwide large cohort of caregivers of patients with KCNQ2-DEE were collected.

This study is based on the collaboration of clinicians with caregivers and patient associations. This approach enabled not only to report the clinical features of KCNQ2-DEE individuals with a wide age range but also to define their relevance with respect to the quality-of-life of their families and caregivers; the data obtained might help in defining more clinically meaningful primary and secondary objectives when planning interventional clinical trials for KCNQ2-DEE patients.

Our study identifies three subgroups of patients based on neurodevelopmental features, regardless of seizure frequency, with different degrees of severity and differences in epilepsy onset and course. A particularly early epilepsy onset could be an early marker of a more severe phenotype.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GC Received speaker honoraria from "GW Pharmaceuticals" and from "Grupo de Trabajo de Epilepsia de la Sociedad Española de Neurología Pediátrica (SENEP)". All remaining authors declare no conflict of interests.

Acknowledgements

We would like to extend our thanks to Mrs. Sylvia Sestini who gave her invaluable suggestions for the paper form and data presentation. This received no specific funding.

We would like to thank especially the EJP-RD Treat KCNQ consortium for harboring the spirit of this study and for further developing better treatments for potassium channel-related disorders.

Prof. F. Darra was funded under the National Recovery and Resilience Plan (NRRP), Mission 4 Component 2 Investment 1.3 - Call for tender No. 341 of 15/03/2022 of Italian Ministry of University and Research funded by the European Union – NextGenerationEU; Project code PE0000006, Concession Decree No. 1553 of 11/10/2022 adopted by the Italian Ministry of University and Research, CUP D93C22000930002, "A multiscale integrated approach to the study of the nervous system in health and disease" (MNESYS).

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

References

[1] Nappi P, Miceli F, Soldovieri MV, Ambrosino P, Barrese V, Taglialatela M. Epileptic channelopathies caused by neuronal Kv7 (KCNQ) channel dysfunction. Pflugers Arch 2020;472:881–98. https://doi.org/10.1007/s00424-020-02404-2.

[2] Weckhuysen S, Ivanovic V, Hendrickx R, van Coster R, Hjalgrim H, Moller RS, et al. Extending the KCNQ2 encephalopathy spectrum: Clinical and neuroimaging findings in 17 patients. Neurology 2013;81:1697–703. https://doi.org/10.1212/01.wnl.0000435296.72400.a1.

[3] Berg AT, Mahida S, Poduri A. KCNQ2 -DEE: developmental or epileptic encephalopathy? Ann Clin Transl Neurol 2021;8:666–76. https://doi.org/10.1002/acn3.51316.

[4] Cohen SR, Helbig I, Kaufman MC, Schust Myers L, Conway L, Helbig KL. Caregiver assessment of quality of life in individuals with genetic developmental and epileptic encephalopathies. Dev Med Child Neurol 2022:1–8. https://doi.org/10.1111/dmcn.15187.

[5] Leonard H, Junaid M, Wong K, Demarest S, Downs J. Exploring quality of life in individuals with a severe developmental and epileptic encephalopathy, CDKL5 Deficiency Disorder. Epilepsy Res 2021;169:. https://doi.org/10.1016/j.eplepsyres.2020.106521106521.

[6] lo Barco T, de Gaetano L, Santangelo E, Bravi T, Proietti J, Cantalupo G, et al. SYNGAP1-related developmental and epileptic encephalopathy: The impact on daily life. Epilepsy Behav 2022;127:108500. https://doi.org/10.1016/j.yebeh.2021.108500.

[7] Miceli F, Soldovieri MV, Ambrosino P, Barrese V, Migliore M, Cilio MR, et al. Genotype-phenotype correlations in neonatal epilepsies caused by mutations in the voltage sensor of Kv7.2 potassium channel subunits. Proc Natl Acad Sci U S A 2013;110:4386–91. https://doi.org/10.1073/pnas.1216867110.

[8] Millichap JJ, Miceli F, de Maria M, Keator C, Joshi N, Tran B, et al. Infantile spasms and encephalopathy without preceding neonatal seizures caused by KCNQ2 R198Q, a gain-of-function variant. Epilepsia 2017;58:e10–5. https://doi.org/10.1111/epi.13601.

[9] Mulkey SB, Ben-zeev B, Nicolai J, Carroll JL, Grønborg S, Jiang Y, et al. HHS Public Access 2018;58:436–45. https://doi.org/10.1111/epi.13676.Neonatal.

[10] Ko A, Jung DE, Kim SH, Kang HC, Lee JS, Lee ST, et al. The efficacy of ketogenic diet for specific genetic mutation in developmental and epileptic encephalopathy. Front Neurol 2018;9:1–9. https://doi.org/10.3389/fneur.2018.00530.

[11] Miceli F, Soldovieri MV, Joshi N, Weckhuysen S, Cooper E. KCNQ2 -Related Disorders Summary Genetic counseling GeneReview Scope 2020:1–25.

[12] Xiao T, Chen X, Xu Y, Chen H, Dong X, Yang L, et al. Clinical Study of 30 Novel KCNQ2 Variants/Deletions in KCNQ2-Related Disorders. Front Mol Neurosci 2022;15. https://doi.org/10.3389/fnmol.2022.809810.

[13] Beck VC, Isom LL, Berg AT. Gastrointestinal Symptoms and Channelopathy-Associated Epilepsy. J Pediatr 2021;237. https://doi.org/10.1016/j.jpeds.2021.06.034. 41–49.e1.