NEW EVIDENCE ON THE OUTCOME OF KCNQ2 PATIENTS

THE IMPACT ON FAMILIES' LIVES FROM THE FIRST EUROPEAN QUESTIONNAIRE

European KCNQ2 Association

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NOTE

Source of information and data mentioned in this document: Epilepsy & Behavior 142 (2023) 109153 “Clinical Characteristics of 80 subjects with KCNQ2-related encephalopaty: Results from a family-drivven survey”.

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INTRODUCTION

KCNQ2 variants are associated with a wide spectrum of disorders. The comorbidities have rarely been described as well as their impact on the lives of patients and their families has not yet been studied.

80 PATIENTS

40 MALES

14 COUNTRIES

7.6 AVERAGE AGE

Starting from a collaboration among caregivers from several international family associations, a questionnaire was developed to investigate the onset and frequency of epileptic seizures, anti epileptic drugs, hospitalization, developmental stages, and comorbidities.
Responses were collected from 80 patients, 40 males from 14 countries. Average age 7.6 year.
The document shows the results of the first European survey of patients with KCNQ 2. We were able to identify three different clusters of varying severity (Milder, Severe, Profound), based on neurodevelopmental characteristics and symptoms, excluding epilepsy. Patients belonging to a higher severity cluster had a higher average number of comorbidities, with a greater impact on families. The study also shows that patients belonging to different clusters had a different onset and course of epilepsy. Thanks to the caregivers who administered the questionnaire and a team of neuropsychiatrists who analyzed the data, it is now possible to define the impact of the disease on the lives of patients and families. This could also help to identify new primary and secondary outcomes in addition to epileptic seizures in future studies.

GENETICS

80%

*De novo** variant

6%

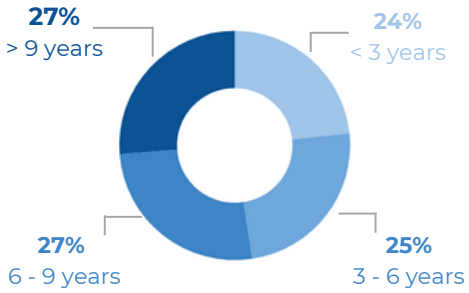
Inherited mutation

14%

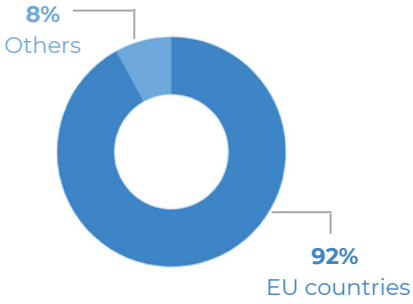
No information

*A **de novo** mutation is any mutation or alteration in the genome of any organism (human, animal, plant, microbe, etc.) that has not been inherited from their parents.

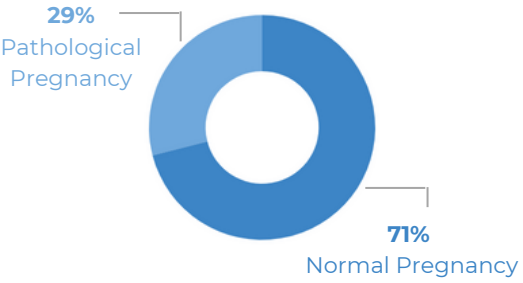
MAIN FEATURES OF THE PATIENTS



Children's age



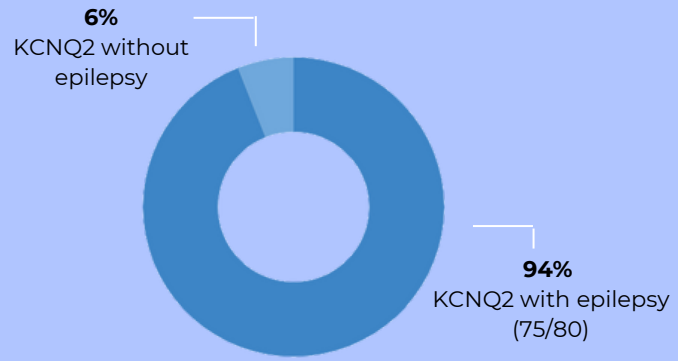
Nationality

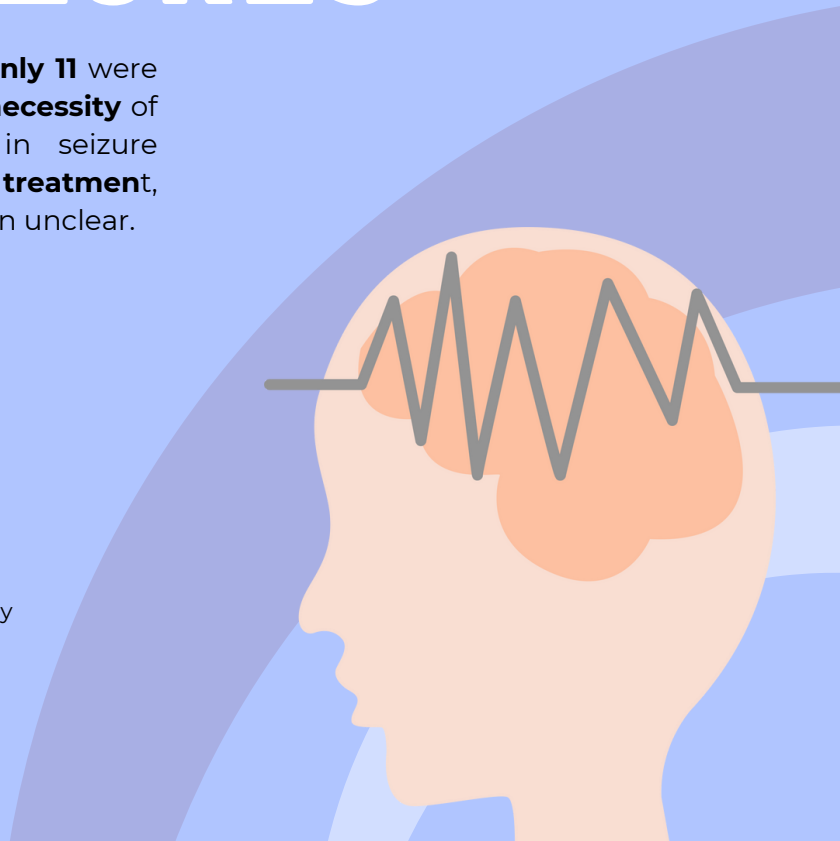


Quality of the Pregnancy

ABOUT SEIZURES

55% seizure free at the time of survey BUT **only 11** were **untreated**, which could suggest the **clinical necessity** of **continued treatment**, despite the drop in seizure frequency. The **reason** for **continuous ASM* treatmen**t, especially in patients older than 13 years, remain unclear.





*ASM (Anti-seizure Medication)

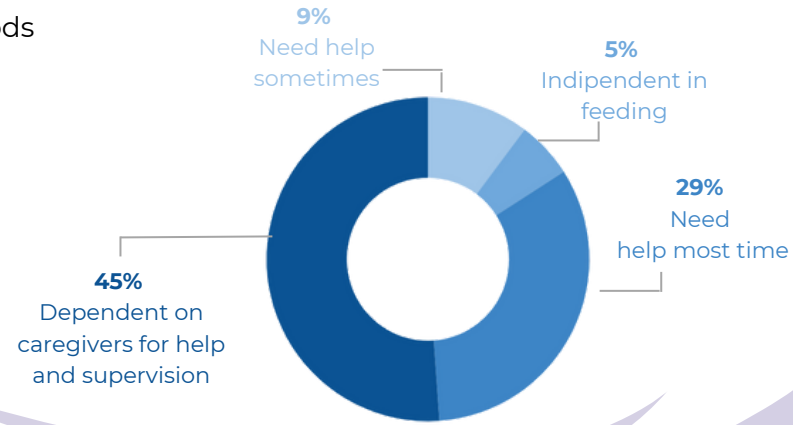
NEUROPSYCHOLOGICAL DEVELOPMENT

- AUTISM was diagnosed in 14% of cases
- 54% Poor social relationship of the child with peers
- 44% fair or good social relationship

FEEDING

- 94% were fed by mouth (75 children)
- 44% following a free diet
- 49% consuming semi-solid foods

FED BY MOUTH



MOTOR SKILLS

< 2 YEARS

- 44% compared to their peers (4/9)
- 12% slightly delayed (1/9)
- 44% moderately to severely delayed (4/9)

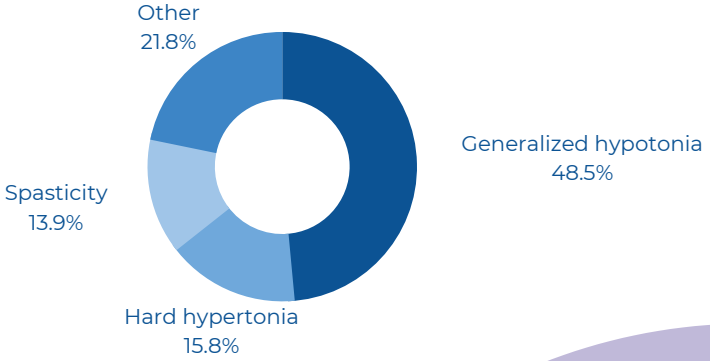
>2 YEARS

- 25% could not keep their heads up (18/71)
- 15% could with support (11/71)
- 5% could sit down on their own but not stand up and walk indipendently(4/71)
- 15% could stand up and walk with aid (11/71)
- 38% walk indipendently (27/71)

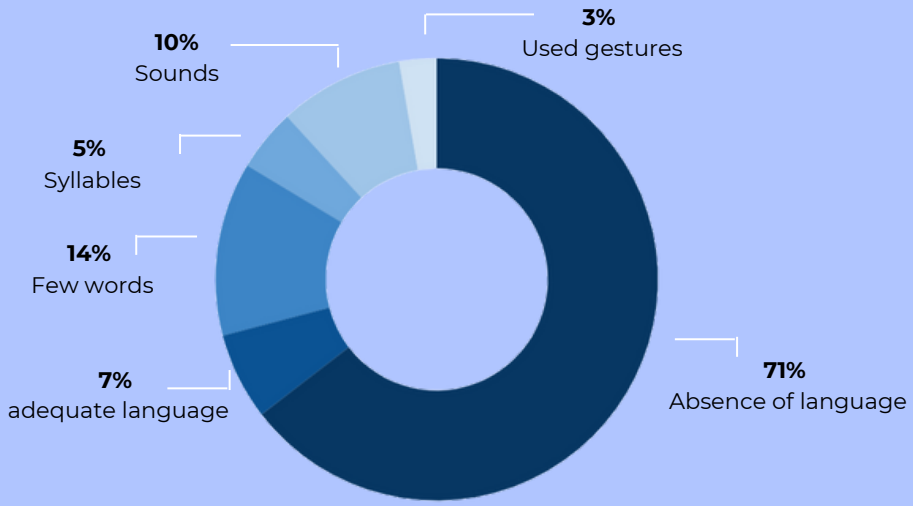
SPHINCTER CONTROL

- 75% unable (45/60)
- 3% alert when needed (2/60)
- 21% could retain control day and night (13/60)

MUSCLE TONE



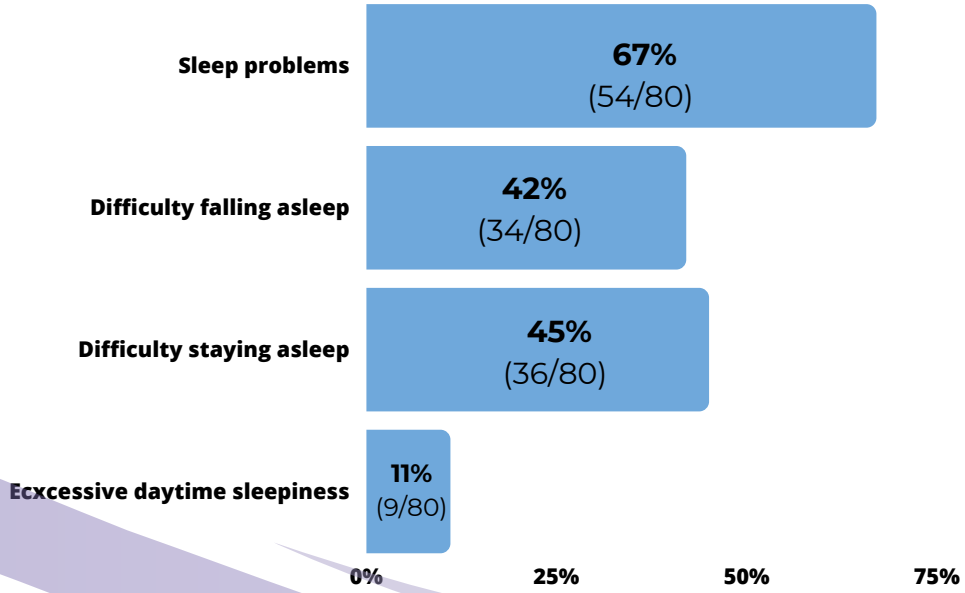
LINGUISTIC SKILLS



Note: 71 responses

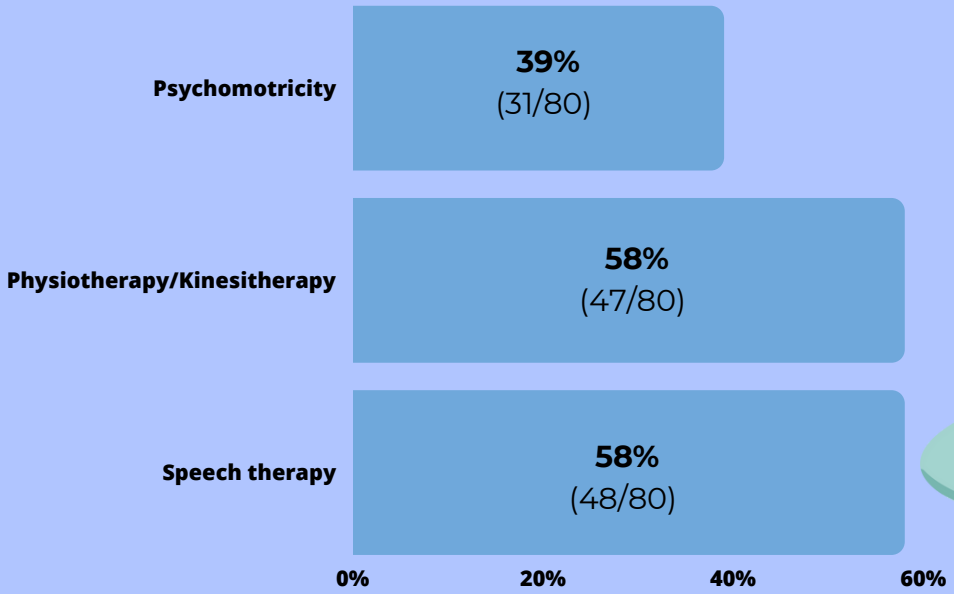
SLEEP

- **24%** of **families** used a **specific medication** to **facilitate falling asleep**
- Only **rarely caregivers** stated a **clear relationship** beetween **sleep and the recurrence** of **seizures**



REHABILITATION

40% undertook daily activities like sport, art, music therapy, equine-assisted therapy.



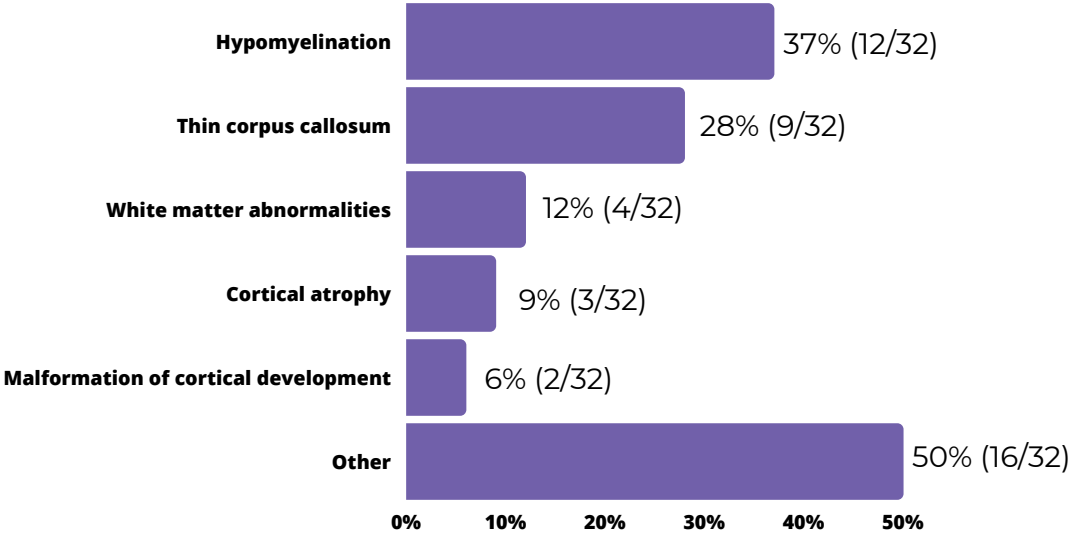
CAREGIVERS' PERSPECTIVE

The issues that affected most the well-being of their child were:

- **developmental delay** 14% (11/80)
- **movement disorder** 11% (9/80)
- **seizures** 7% (6/80)
- **muscle tone** 6% (5/80)
- **language** 5% (4/80)
- Other cited issues were **autism**, **pain**, **gastrointestinal issues**, **respiratory problems**, **vision**, **sleep issues**, **feeding issues**, and **osteoarticular problems**.

MAGNETIC RESONANCE IMAGING

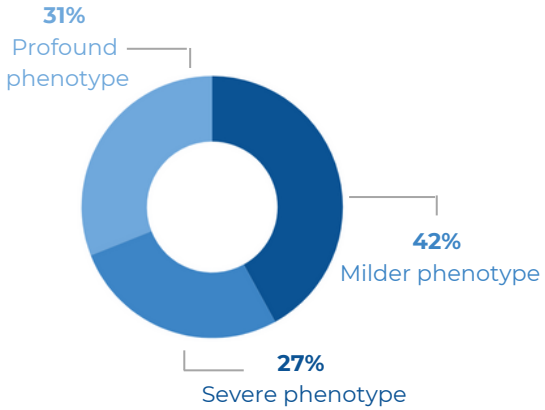
The MRI found **an abnormality in 43%** (32/75) of cases. Among these findings, families listed: hypomyelination in 37% (12/32), white matter abnormalities in 12% (4/32), cortical atrophy in 9% (3/32), malformation of cortical development in 6% (2/32), thin corpus callosum in 28% (9/32), and other nonspecific abnormalities in 50% (16/32) of the patients.



CLUSTER ANALYSIS

A cluster analysis was considered with regard to motor skills, feeding abilities, muscle tone, language, presence of autism and motor stereotypies. These variables were analysed in the 71 patients over 2 years of age in order to obtain a more homogeneous developmental phenotype with comparable stages in motor and language development.

Milder phenotype: ability to walk, feeding by mouth with a diet of varying consistency, normal muscle tone or mild hypotonia and productive language. Lower incidence of epilepsy.
Severe phenotype: ability to sit and stand independently but not to walk, feeding on a diet of semi-solid consistency, spastic muscle hypertonia and language characterised by sounds or syllables. Lower incidence of autism diagnosis. Epilepsy in almost all cases.
Profound phenotype: inability to hold head up, feeding on semi-solid diet or PEG, variable muscle tone with hypotone and hypertone. All patients were non-verbal. None of them were diagnosed with autism, all patients were epileptic.



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.

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 average age at the last seizure was higher in patients in the Severe cluster.

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.

Thank you to all the families!
This major contribution to research
would not have been possible
without your valuable support.

European KCNQ2 Association

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