EPILEPSY IN YOUNG CHILDREN (EPYC)
STUDY PROTOCOL

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The Epilepsy in Young Children Study

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1. Scientific aims and study design

The Epilepsy in Young Children (EPYC) Study is a case-control study of childhood epilepsy nested within the Norwegian Mother, Father and Child Cohort Study (MoBa).[1,2] Investigations are based on MoBa questionnaire data, data from the Medical Birth Registry and data collected specifically for the EPYC Study. The scientific aims of the study are to:

(1) Identify cases of epilepsy in MoBa and use clinical interviews and medical record information to validate diagnoses and describe seizure, MRI and EEG characteristics.
(2) Describe developmental trajectories and impairments in children with epilepsy.
(3) Use cluster analysis to determine the prevalence of epilepsy phenotypes on the basis of seizure, MRI and EEG characteristics, and developmental trajectories.
(4) Investigate prenatal, perinatal and early life risk factors for epilepsy.

2. Study organization

The EPYC Study was initiated in 2012. It is conducted in collaboration between the Norwegian Institute of Public Health (NIPH), the National Center for Epilepsy (NCE) at Oslo University Hospital and the Muir Maxwell Epilepsy Centre at University of Edinburgh (UoE). A support network of paediatricians has been established to facilitate the collection of data from medical records. The first round of data collection took place in 2012-2015 and was funded by the Research Council of Norway. A PhD project, which was funded by the Regional Health Authority of South-East Norway, generated four publications.[1,3-5]

3. Ethics and regulatory approvals

MoBa is regulated under the Norwegian Health Registry Act. Participation in MoBa is based on written informed consent. The consent includes permission to perform linkages to health registries and collect data from medical records. The EPYC Study has approval from the Regional Committee for Medical and Health Research Ethics for South-East Norway (reference no. 20478). The telephone interviews conducted by the EPYC Study was based on a separate written consent.

4. Identification and characterization of epilepsy cases

Epilepsy is defined as two or more unprovoked seizures occurring at least 24 hours apart. MoBa participants are defined as potential epilepsy cases if meeting one or both of the following criteria:

a. A record of epilepsy and/or status epilepticus diagnoses in the Norwegian Patient Registry (NPR) (ICD-10 codes G40.X and/or G41.X).
b. Parental report of epilepsy or afebrile seizures in the MoBa questionnaires.

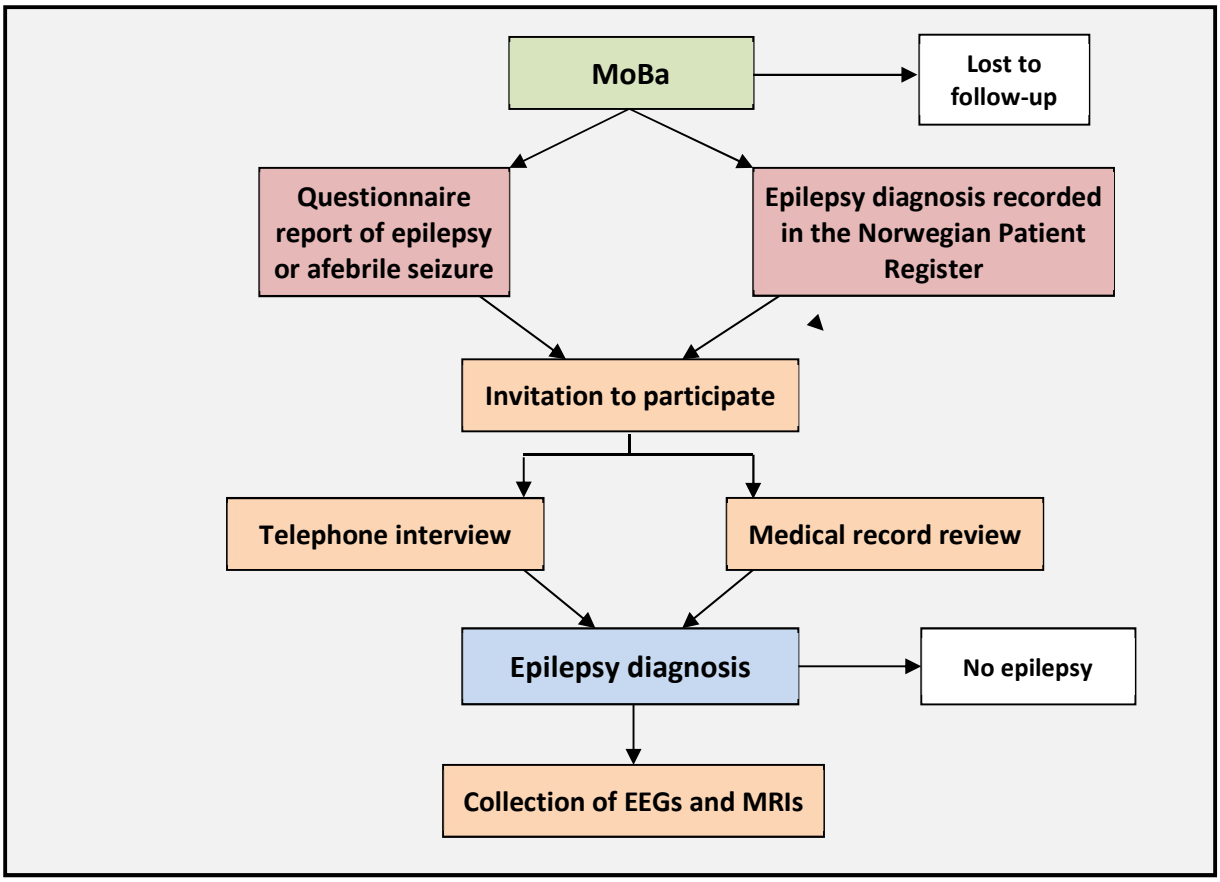
The NPR collects data from all hospitals and outpatient clinics in Norway, starting from 2008. The MoBa questionnaires included specific questions about epilepsy at ages 5 and 7 years.

During the first round of data collection, the EPYC Study collected the following data:

a. A telephone interview with the parents to verify the diagnosis, determine the type of seizures and investigate psychological functioning and quality of life.
b. Clinical data from medical records: Medical and developmental history, age of onset of seizures, description of seizures, frequency of seizures, investigation results, type of treatment, treatment response and comorbidities.
c. Copies of magnetic resonance imaging (MRI) brain scans, if available.
d. Copies of electroencephalogram (EEG) recordings, if available.

The second round of data collection, which is planned for 2021-2022, will only include clinical data from medical records.

Figure 1 **Overview of EPYC case identification procedures**



5. The EPYC data collection template

Clinical data are collected using the template developed for epilepsy research at the University of Melbourne (Appendix 2). This template is designed as an interview and has been validated for seizure classification.[6] The EPYC data collection template (Appendix 3) is also structured as an interview, but it is suitable for extraction of data from medical records, too. The seizure-specific questions are identical to the ones of the Melbourne protocol, but the following modifications were made to the other sections:

- The section about pregnancy, birth, and neonatal complications was shortened, because these data are already available through MoBa and the MBRN.
- Questions that are inappropriate for children were removed.
- Questions about comorbid disorders and other difficulties were changed to include those disorders and developmental difficulties that are most frequent in children with epilepsy.

The following (non-seizure) questions were added:

- Questions about follow-up from health services, educational services and other welfare/social services.
- Questions about the use of rescue medications at home.
- Questions about results of EEG and MRI investigations and neuropsychological and genetic evaluations (the Melbourne protocol just asks whether such investigations have been done, not about the results).
- Selected quality-of-life questions from the Quality of Life in Epilepsy Inventory (QOLIE).[7]
- The Strengths and Difficulties Questionnaire (SDQ) (25 questions).[8]

Kari M. Aaberg, who is a paediatrician and child epileptologist, translated the Melbourne template from English into Norwegian. The translation was then controlled and edited by Camilla Lund Søraas and Pål Surén. A reverse translation (from the Norwegian version and back into English) was conducted by Lucy Robertson, who is a professor at the Norwegian School of Veterinary Science and has English as her first language.

The EPYC template is designed for use by physicians. It was piloted on 30 patients at the NCE in the autumn of 2012. The experiences from the pilot study, plus the reverse translation, was used to edit and finalize the template. All physicians using the template must complete interviews with at least 10 patients at the NCE before using it for study purposes.

6. Classification of seizures and syndromes

Epileptic seizures and epilepsy syndromes are classified both according to the classification system devised the International League Against Epilepsy (ILAE). The classification is conducted according to both the old classifications from 1981/1989[9,10] and the new classifications from 2017.[11,12]

If the record review and/or the interview reveal that the child does not meet the research criteria for an epilepsy diagnosis, a separate form (Appendix 4) is used to investigate why the G40.X/G41.X diagnoses was recorded in the NPR, or why the parents have reported epilepsy or afebrile seizures in the questionnaires. This form includes information about whether the child ever had seizures (and if so, what type of seizures), other diagnoses, EEG findings, MRI findings, treatment with antiepileptic drugs, etc.

7. Reviews of MRI scans

During the first round of data collection, MRIs are assessed qualitatively by two paediatric neuroradiologists using a standard proforma from the Great Ormond Street Children's Hospital (Appendix 5). The radiologists were blinded to the clinical information and EEG results. They systematically reviewed all brain structures known to be associated with developmental abnormalities: ventricles, corpus callosum, gray and white matter, limbic system, basal ganglia, brainstem, and cerebellum. Structures were classified according to morphology and signal return on T1/T2 weighted images acquired in a combination of imaging planes. The radiologists worked independently of each other, and inter-rater reliability was quantified by kappa scores.

8. Reviews of EEG recordings

During the first round of data collection, the date and type of each EEG exam were recorded, and the results were summarized. If more than one EEG was available, the researcher selected which EEG to be copied according to the following priority list:

1. EEG with seizures (before or after the start of treatment)
2. EEG with recording of epileptic activity *before* the start of treatment
3. EEG with recording of epileptic activity *after* the start of treatment
4. EEG with long-term monitoring
5. Other EEGs (standard or sleep-deprived)

EEGs were assessed qualitatively by two neurophysiologists using a proforma developed for the London Neurogenetics Database (Appendix 6). They recorded and described epileptic abnormalities, i.e., the localisation/lateralisation of epileptic activity, the frequency and character of the epileptic discharges, whether the epileptic discharges were ictal or non-ictal, and whether the discharges conformed to any particular seizure type and/or epileptic syndrome. The background activity and the presence of non-epileptic abnormalities were also be recorded. Corresponding to the MRI assessments, the neurophysiologists worked independently of each other and were blinded to clinical information and MRI findings. Inter-rater reliability was quantified by kappa scores.

9. Data management

During the first round of data collection, the data were transferred to a paper form, which was then scanned and processed by the MoBa data unit in Bergen, Norway. During the second round of data collection, data will be entered into an Excel database. The data will be converted to SPSS files and made available for researchers with EPYC-specific file IDs. The MoBa and MBRN files available for EPYC researchers have the same EPYC-specific file IDs, so that the EPYC-specific data can be merged with MoBa and MBRN data.

10. Appendices

Appendix 1: The original EPYC study protocol from 2013.
Appendix 2: The template developed for epilepsy research at the University of Melbourne.
Appendix 3: The EPYC data collection template.
Appendix 4: Data collection template for participants who do not meet the research criteria for an epilepsy diagnosis.
Appendix 5: MRI review form.
Appendix 6: EEG review form.

11. References

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