Grant agreement no. 769051

EpiCARE – a network for rare and complex epilepsies

HP-ERN-2016 European Reference Networks / Framework Partnership Agreement

D7.1 Report on usual treatment regimes

Work Package: WP7: Targeted medical therapies

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Table of contents

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1. Version log

Version	Date	Released by	Nature of Change
First version	03.02.2018	R Surges (Bonn)	First version

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2. Definition and acronyms

Acronyms	Definitions
CHD2	Gene for chromodomain helicase DNA binding protein 2
GLUT1	Gene for Glucose transporter 1
KCNQ2	Gene for potassium voltage-gated channel subfamily Q member 2
SCN8A	Gene for the alpha-subunit of the voltage-gated sodium channel type VIII
STXBP1	Gene for syntaxin binding protein 1

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3. Introduction

Recognition of the epilepsies as a group of rare diseases with known aetiologies gives us insight as to the underlying mechanisms involved in seizure generation, and further comorbidities such as cognitive, physical, emotional and behavioural capacities. The correct and timely diagnosis of rare forms of epilepsy is crucial for a tailored, successful treatment. In this context, the workpackage 7 “Targeted Medical Therapies” deals in particular with medically compulsory and future medical treatment regimes in people with rare and complex epilepsies. One of the objectives of WP7 is to investigate the occurrence of rare and complex epilepsies, the applied medical therapies and their outcome in the expert centres and collaborating clinical partners. Such an analysis of the current state is also important in order to estimate the population that can potentially be reached for future trials.

To that end, we aimed at a first step to

- Organize assessment with respect to disease or condition and nomination of leading centre per disease or condition (with WP 2 and V)
- Establish data on usual treatment regimens of different rare and complex epilepsies of EpiCARE partners (status-quo analysis)
- Define research priorities for targeted medical therapies of rare and complex epilepsies (with WP V)

4. Activities carried out and results

Activities carried out

We have carried out a written survey distributed via email to the leads of the participating centres. The questionnaire included the questions on the number of newly diagnosed patients per centre per year of 5 arbitrarily selected diseases and whether the institutions have established protocols for diagnosis and treatment of these entities. Finally, the respondents were asked to specify their particular expertise and scientific interest. In addition to the five selected diseases, the participants were given the opportunity to provide answers to these questions to any other disease(s).

The results were summarized and presented and discussed at the EpiCARE meeting the 3. June 2017 in London.

Results

A total of 18 centres participated in the survey. The number of new patients of each disease entity varied considerably per centre. Mitochondriopathies were the most frequent disease with about 9 newly diagnosed patients per year per centre (figure 1).

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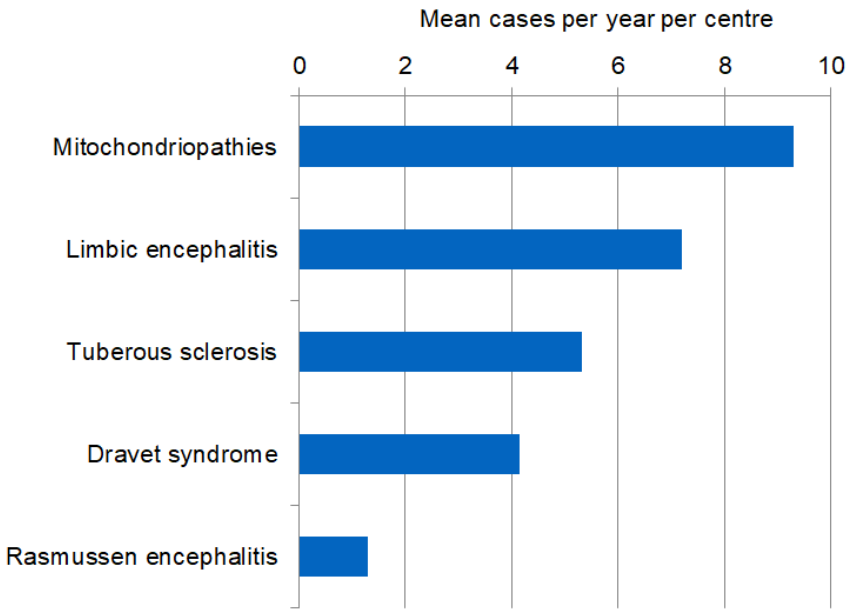

Figure 1. Estimated numbers of new patients with 5 selected rare epilepsies per year per centre. Numbers are given as average of the 18 respondents.

Seven respondents also mentioned the following diseases as causes for epilepsy in their centre:

- One centre epilepsies due to mutations in the GLUT1 gene, Sturge Weber syndrome, neuronal ceroid-lipofuscinosis, myoclonic absence epilepsies
- One centre epilepsies due to channelopathies (KCNQ2 and SCN8A gene)
- One centre progressive myoclonic epilepsies and other metabolic epilepsies
- One centre other genetic epilepsies

Three of the seven respondents did not provide further information.

Surprisingly and in contrast to its frequency, mitochondriopathies were the disease for which the responding centres had on average more seldomly established protocols for diagnosis and treatment (figure 2 and 3), highlighting the need for common guidelines on rare epilepsies.

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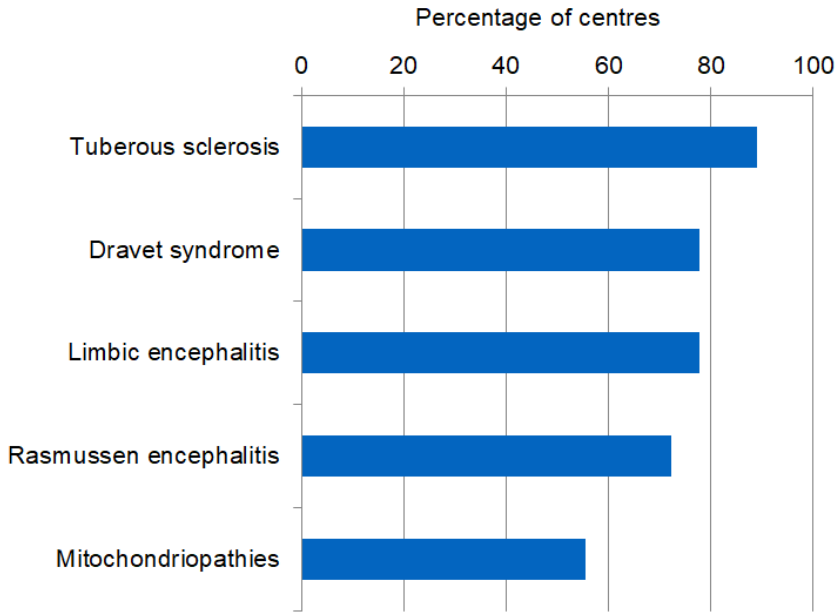

Figure 2. Percentage of centres with established treatment protocols for the 5 selected diseases.

Five participants specified to have established treatment protocols for the other rare diseases as follows:

- One centre for epilepsies due to mutations in the GLUT1 gene, for Sturge Weber syndrome, neuronal ceroid-lipofuscinosis and myoclonic absence epilepsies
- One centre for “Electrical Status in Slow-Wave Sleep”.

The other three centres did not further specify.

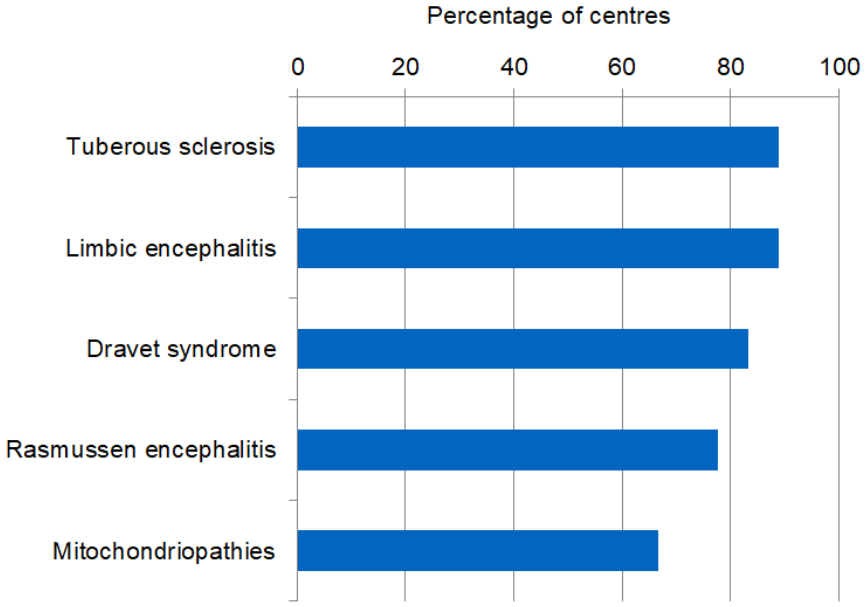

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Figure 3. Percentage of centres with established protocols for diagnostic work-up for the 5 selected diseases.

Eight participants specified to have established protocols for the diagnostic work-up of other rare epilepsies:

- One centre for epilepsies due to mutations in the GLUT1 gene, for Sturge Weber syndrome, neuronal ceroid-lipofuscinosis and myoclonic absence epilepsies
- One centre for presumed genetic epilepsies and “Electrical Status in Slow-Wave Sleep”.
- One centre for channelopathies as rare cause of epilepsy
- One centre for epilepsies due to malformations of cortical development

The other four centres did not provide further specifications.

About two thirds of the responding centres mentioned to have particular expertise of interest in epilepsies due to Dravet syndrome and tuberous sclerosis (figure 4).

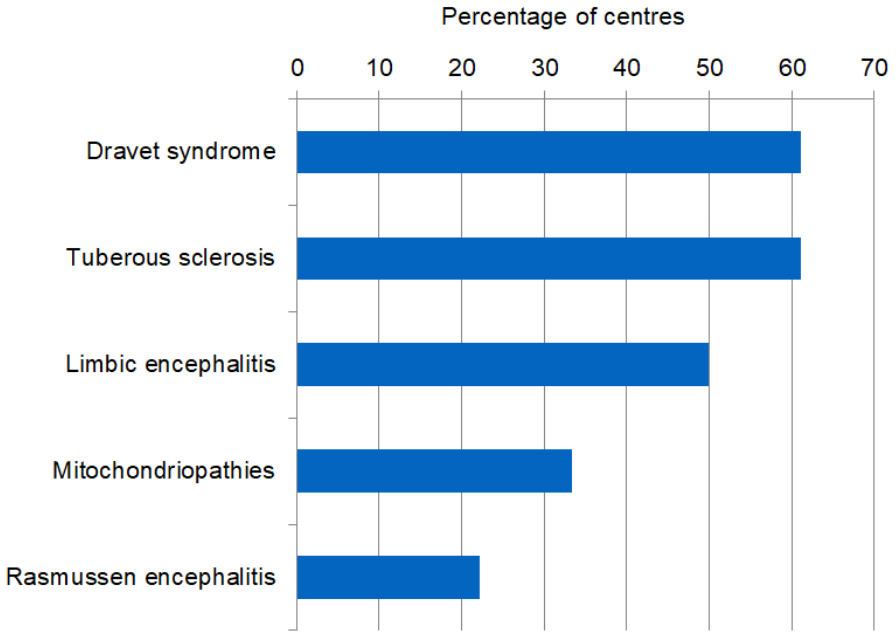

Figure 4. Percentage of centres with expertise or particular interest in 5 selected diseases.

Seven participants specified to have expertise or interest to contribute in the following diseases:

- One centre for epilepsies due to Sturge Weber syndrome and Doose syndrome, neuronal ceroid-lipofuscinosis and myoclonic absence epilepsies
- One centre for monogenic childhood syndromes, focal lesional epilepsies, epilepsy surgery, epileptic encephalopathies (including “Electrical Status in Slow-Wave Sleep”).
- One centre for GLUT1 mutations as rare cause of epilepsy
- One centre for epilepsies due to malformations of cortical development

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- One centre for epilepsies due to hypothalamic hamartomas
- One centre for epilepsies due to other genetic causes
- One centre for drug resistant and rare epilepsy clinical trials

The respondents of this survey had the opportunity to make comments on the workpackage “Targeted Medical Therapies”. Eight respondents suggested the following aspects and points:

- Further genetic epilepsies were specified (duplication in 15q, mutations in the genes CHD2, STXBP1, Angelman-2 syndrome, 22q syndrome, GABA transaminase deficiency)
- Epilepsies due to malformations of cortical development need to be a special category
- Complex epilepsies without diagnosis should be considered
- It will be adequate to approach this subject always on an interdisciplinary basis. Within the diverse Network nodes we need to have similar approaches. It means that a broad discussion about the protocols necessaries to approach and to achieve a syndrome in which the patient drop in, could be started within the EpiCare.

The results were critically discussed at the Epicare meeting the 3. June 2017 in London.

5 Conclusions

The survey provides a realistic estimate of frequencies of selected, newly diagnosed rare and complex epilepsies in the responding centres, which is a prerequisite to plan future epidemiological and therapeutical studies. The survey has also helped to identify the particular interests and expertise of the responding centres, thereby allowing bringing together experts in order to further develop research strategies and guidelines for appropriate diagnosis and treatment.

The present deliverable D7.1 intends to provide a report on usual treatment regimens for rare and complex epilepsies. Maybe the major finding of our survey is that the presence of established protocols for diagnostic and therapeutic procedures in the participating centres strongly depends on the disease and that for many forms of rare and complex epilepsies established protocols appear to be completely lacking. This finding highlights the need for more knowledge, controlled clinical trials and common guidelines to improve the clinical care of affected people. Therefore, this deliverable will prompt further work to be done in year 2, taking into account the knowledge gained from this survey as well as other surveys from year 1 (such as surveys and advancements in the workpackages on laboratory diagnostics, EEG, neonatal seizures and clinical trials) in order to be able to develop a more coherent picture of treatment regimes in various EpiCARE centres.

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6 Annex 1

The following questionnaire was used to organize the assessment with respect to disease condition and nomination of leading centre per disease or condition, get data on usual treatment regimens of different rare and complex epilepsies of EpiCARE partners (status-quo analysis) and to define research priorities for targeted medical therapies of rare and complex epilepsies (with WP V) in EpiCARE centres.

	Limbic encephalitis	Rasmussen encephalitis	Dravet syndrome	Tuberous sclerosis	Mitochondriopathies	Other (please list)
Estimated annual number of patients with						
Do you have an established treatment plan for ...						
Do you have an established diagnostic workup for ...						
Where do you see your particular expertise and/or to what disease-group would you like to contribute as part of the leading subgroup ?						

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