Grant agreement no. 811537

EpiCARE – a network for rare and complex epilepsies

HP-ERN-2017 European Reference Networks / Framework Partnership Agreement (FPA 739537)

D3.3 Open access publication on imaging standards and guidelines for rare and complex epilepsies
D3.4 Development of secure neuroimaging database for patients and controls

Work Package: 3

Due date of deliverable: month 12

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Lead beneficiary for this deliverable: 28 EpiCARE centres
Contributors: *Prof Kees Braun – Prof Petr Marusic*

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Dissemination Level		
PU	Public	PU

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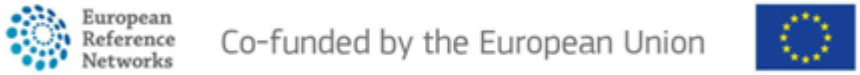

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1. Version log

Version	Date	Released by	Nature of Change
1	27-02-2019	K. Braun (UMCU), P. Marusic (NB MOTOL)	First version

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2. Definition and acronyms

Acronyms	Definitions
EpiCARE	European Reference Network of Rare and Complex Epilepsies
E-pilepsy	Cross-country epilepsy surgery network with the aim of helping clinicians with the pre-surgical evaluation of epilepsy cases
CURRY	CURRY Neuroimaging Suite software
CMPS	Clinical Patient Management System
MAP	morphometry analysis program
MRI	Magnetic resonance imaging
SPECT	Single Photon Emission Computed Tomography
PET	Positron-emission tomography

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3. Introduction

D3.3 "open access publication on imaging standards and guidelines"

Aims are: to enable exchange of best practice and promote harmonisation of care in the neuroimaging of rare and complex epilepsies (guidelines and standards), and to have imaging standards for rare and complex epilepsies translated into a care pathway. In general, the work package will ensure that:

1) currently available guidelines and recommendations on neuroimaging will be placed on the open EpiCARE website
2) recent systematic reviews on imaging (E-PILEPSY output) will be summarized on the open EpiCARE website
3) the EpiCARE consortium will produce expert-opinion/consensus recommendations for imaging in specific epilepsy subtypes and populations

D3.4 "development of secure neuroimaging database for patients and controls"

Aims are: to create a database of anonymized neuroimaging findings of specific rare and complex epilepsies and of healthy control images.
The register of patients with specific epilepsy syndromes or etiologies (e.g. neurometabolic syndromes, genetic syndromes, inflammatory epilepsies) may serve to enable the collection and review of images to characterize imaging findings and for pattern recognition, both for scientific and clinical purposes.
In order to enable the development and use of a centralized web-based imaging post-processing tool for presurgical evaluation, we need a large collection of healthy volunteer brain MRI's, from different scanners, field strengths, and ages. Therefore, this deliverable runs in parallel with the development, optimization and implementation of a new MAP (morphometry analysis program) tool, to be implemented in CURRY on a central IT platform.

4. Activities carried out and results

A) Activities directly related to this year's deliverables

D3.3 "open access publication on imaging standards and guidelines"

Activities

We will publish on the EpiCARE website a document that consists of:
- a) **survey results** on imaging in the current and previous (pilot) network (E-PILEPSY 2014, EpiCARE 2017)
- b) a summary of the currently available and **published guidelines/recommendations** on imaging in epilepsy
- c) the results of the E-PILEPSY **systematic reviews** on MRI (field strength/sequences) and on PET/SPECT (work in progress)

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In the coming year we aim to produce new, EpiCARE expert-opinion and consensus-based imaging guidelines in epilepsy. We have recently circulated a survey with questions regarding specific sequences in specific situations. Based on input from its responses we will produce a list of recommendations, that will be further commented on by the expert-group members, in order to reach consensus. A first meeting with experts was organized. When this is finalized, recommendations will be published on the EpiCARE website.

Results

- Document containing a), b) and c) is finalized and will be placed online. See below. This deliverable has been achieved.
- New recommendations (not part of the initial deliverable, to be completed next year): there is good progress, with a first survey having been circulated, and input collected. A first expert meeting on the topic has been successfully attended (in person and online) by a group or neuroimaging experts (Febr. 2019).

Additional information: text of neuroimaging standards and guidelines, online available

I. ***Survey 2014: use of imaging in E-PILEPSY epilepsy surgery centers in Europe***

Mouthaan BE, Rados M, et al. Current use of imaging and electromagnetic source localization procedures in epilepsy surgery centers across Europe. Epilepsia 2016;57:770-776

Summary:

- *Survey among 25 centers, 2014, response rate 94% (24 centers)*
- *15 centers (63%) use 3T for standard MRI epilepsy protocol, 3 others have 3T available for patients who are MRI-negative at lower field*
- *1 center has 7T available for presurgical imaging*
- *MRI protocols of only 6 centers (25%) meet the published recommended criteria for slice orientation and thickness for each of the sequences (3D volume T1 isotropic resolution <= 1mm and axial T2, coronal T2, axial FLAIR and coronal FLAIR each with slice thickness <= 3mm). 50% of all centers perform all MRI sequences with slice orientation as recommended in the guidelines (see ad III.)*
- *8/24 centers perform MRI morphometric analysis for post-processing purposes*

II. ***Survey 2017: use of imaging in EpiCARE centers in Europe***

Summary:

- *Survey among 28 centers (22 treat adults only), 2017, response rate 93% (26 centers)*
- *20 centers (77%) use 3T for their standard MRI epilepsy protocol in children, 22 (90%) centers in adults. For presurgical evaluation 3T is available in all centers for adults, and in 21/26 (81%) centers for children*
- *MRI protocols of most of the centers 18 (82%) in adults, and 17 (71%) in children, meet the published recommended criteria for slice orientation and thickness for each of the sequences (3D volume T1 isotropic resolution <= 1mm and axial T2, coronal T2, axial FLAIR and coronal FLAIR each with slice thickness <= 3mm). 50% of all centers perform all MRI sequences with slice orientation as recommended in the guidelines (see ad III.)*
- *17/26 centers (65%) perform some sort of MRI morphometric analysis for post-processing purposes*

III. ***Published recommendations on structural imaging in epilepsy***

Summary of recommendations

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Structural imaging should be performed in all patients, both children and adults, with newly diagnosed epilepsy. Only in patients with a definite electroclinical diagnosis of idiopathic generalized epilepsy (benign myoclonic epilepsy of infancy, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy) or benign epilepsy of childhood with centrotemporal spikes, structural imaging can be omitted. Structural imaging is especially recommended in patients with localization-related epilepsy, when epilepsy classification is in doubt, when a symptomatic generalized epilepsy syndrome is suspected, when there is a focal deficit on neurological or neuropsychological examination, in the case of raised intracranial pressure, status epilepticus or atypical course of the above-mentioned exceptions, and in children with epilepsy under the age of two years or with developmental regression.[1-3]

The purpose of structural imaging is to establish etiology, provide a prognosis and direct treatment.[1,2]

Magnetic resonance imaging (MRI) is considered mandatory as a primary imaging modality and epilepsy surgery should never be considered without performing an MRI.[1,2,4-6] Computed tomography (CT) is only appropriate in the acute emergency situation, or when MRI cannot be performed because of technical reasons (i.e. in a patient with a cardiac pacemaker), recognizing that some symptomatic causes for epilepsy (MTS, small tumors or subtle FCD) might be missed.[1,7]

Regarding the precise MRI protocol, most published recommendations agree that this should include a three-dimensional (3D) T1-weighted sequence, coronal and axial T2-weighed sequences and coronal and axial fluid-attenuated inversion recovery (FLAIR) sequences.[2,3,5,8-11] Some specifically advise a slice orientation for the T2 and FLAIR in hippocampal angulation.[8] For 3D T1, voxel size should not exceed 1 mm. For T2 and FLAIR, slice thickness should not exceed 3 mm.[3,8]

Other sequences – that are mentioned in the different published recommendations but of which the exact added diagnostic value remains unclear – include hemosiderin/calcification sensitive sequences, diffusion-weighed imaging (DWI), inversion recovery (IR), proton density (PD), 3D FLAIR, 3D double inversion recovery (DIR), susceptibility weighted imaging (SWI) and magnetization transfer (MT).[3,8,12] All recommendations agree that gadolinium enhanced MRI should only be performed when a tumor, vascular malformation, inflammation or infection is suspected.[2,3,8]

In children under the age of two years, incomplete myelination may cause lesions not to be visible on MRI. Some guidelines recommend including a HR T2 sequence in the protocol for this reason or a SWI sequence, and mention that FLAIR and PD sequences might be less helpful due to this lack of myelination. Repeated imaging after 1-2 years is also advised in young children.[2,6,8]

Regarding MRI field strength, 1.5T is considered minimal, and some authors have recommended to use higher field strengths, such as 3T.[3,9] A minimum of an eight-channel head coil is also recommended.[3]

MRI should be interpreted in the context of clinical semiology and EEG findings by a radiologist who is experienced in epilepsy imaging. Should a lesion not be identified on the epilepsy protocol MRI, a repeat MRI using a higher-resolution targeted to the suspected epileptogenic area should be performed.[3]

References:

1. *Recommendations for neuroimaging of patients with epilepsy. Commission on Neuroimaging of the International League Against Epilepsy. (no authors listed). Epilepsia 1997;38:1255-1256.*
2. *Gaillard WD, Chiron C, Cross JH et al. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia 2009;502147-2153.*
3. *Martinez-Rios C, McAndrews MP, Logan W et al. MRI in the evaluation of localization-related epilepsy. J Magn Reson Imaging 2016;44:12-22.*

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4. *Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia 2014;55:507–518.*
5. *Guidelines for neuroimaging evaluation of patients with uncontrolled epilepsy considered for surgery. Commission on Neuroimaging of the International League Against Epilepsy. (no authors listed). Epilepsia 1998;39:1375-1376.*
6. *Cross JH, Jayakar P, Nordli D et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. Epilepsia 2006;47:952-959.*
7. *Harden CL, Huff JS, Schwartz TH et al. Reassessment: neuroimaging in the emergency patient presenting with seizure (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2007;69:1772-1780.*
8. *Wellmer J, Quesada CM, Rothe L et al. Proposal for a magnetic resonance imaging protocol for the detection of epileptogenic lesions at early outpatient stages. Epilepsia 2013;54:1977-1987.*
9. *Steinhoff BJ, Bacher M, Bucurenciu I et al The impact of guidelines on the quality of MRI diagnostics in adult patients referred to a tertiary epilepsy center. J Neurol 2013;260:3174-3175.*
10. *Jackson GD, Badawy RA. Selecting patients for epilepsy surgery: identifying a structural lesion. Epilepsy Behav 2011;20:182–189.*
11. *Obeid M, Wyllie E, Rahi AC, et al. Approach to pediatric epilepsy surgery: state of the art, Part I: general principles and presurgical workup. Eur J Paediatr Neurol 2009;13:102–114.*
12. *Deblaere K, Achten E. Structural magnetic resonance imaging in epilepsy. Eur Radiol 2008;18:119–129.*

IV. *Systematic review of the added diagnostic value of higher field strength and newer MR sequences in presurgical evaluation*

Rados M, Mouthaan BE, van Eijsden P, Braun KP et al. The E-PILEPSY consortium. Manuscript in preparation

Summary

Field strength

- *3T MRI has an added value of 21.6% detection rate in 1.5T MR-negative patients with focal epilepsy (GRADE very low [+])*
- *3T MRI has no added value over 1.5T in patients with mTLE/HS (GRADE low [++])*
- *7T MRI has an added value of 28.6% detection rate in 1.5/3T MR-negative patients with focal epilepsy (GRADE very low [+])*

General sequences

- *A dedicated epilepsy MR-protocol has a lesion detection rate of 86.2% (subgroup mTLE/HS: 83.6%, subgroup FCD: 85.6%, subgroup focal epilepsy with variable pathology: 88.9%) (GRADE very low [+])*
- *General T1-sequences have a lesion detection rate of 83.4% in patients with mTLE/HS (GRADE very low [+])*
- *General T2-sequences have a lesion detection rate of 89.2% in patients with mTLE/HS (GRADE very low [+])*
- *FLAIR has a lesion detection rate of 90.2% in patients with mTLE/HS (GRADE very low [+])*

Newer / advanced sequences

- *Quantitative ADC measurements have a lateralizing value of 33.3% in conventional MR-negative patients with unilateral HS (GRADE very low [+])*

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- *Hippocampal T2 relaxometry has a lateralizing value of 40.7% in conventional MR-negative patients with unilateral HS (GRADE very low [+])*
- *There is no added localizing value of T1 + gado in conventional MRI-negative patients with refractory focal epilepsy (GRADE low [++])*
- *7T T2* and SWI have no added value in mTLE/HS, but 7T T2* does have an added value of 16.7% in patients with FCD (GRADE very low [+])*
- *There is no evidence on the added value of DTI with histopathology as a reference standard*
- *Diagnostic value of DTI when compared to other reference standards:*
    - *DTI has a lateraling value in 62.6% in conventional MRI-negative patients with unilateral HS (GRADE very low [+])*
    - *MD lesion detection rate is 41.2% in conventional MRI-negative patients with refractory partial epilepsy (GRADE very low [+])*
    - *FA lesion detection rate is 26.6% in conventional MRI-negative patients with refractory partial epilepsy (GRADE very low [+])*
    - *DTI has an added detection rate of 40.2% in conventional MRI-negative patients with refractory partial epilepsy, but a false detection rate of 28.8% (GRADE very low [+])*

V. ***Systematic review on added value of PET/SPECT in presurgical evaluation***

Work in progress, Sulc V, Marusic P

D3.4 "development of secure neuroimaging database for patients and controls"

Activities

- during year 2018, the CMPS was tested for its ability to upload individual patient's scans, and for its viewer system. Both are fully functional. In cooperation with the ERN IT platform refining of the viewing of neuroimaging data is possible. Access to data is limited to ERN members and ERN guests with EU login. Furthermore, an authorization request to use the CPMS is also needed.
- a survey was circulated to inventorize the centers' available databases of patient and control MR images.
- an MRI expert group meeting was organized in Febr 2019, to discuss issues of neuroimaging recommendations, and of healthy control scan collection and databases
- a close cooperation with the Human Brain Project was also discussed using their Medical Informatic Platform, which is able to perform federated analysis of data distributed across several hospitals, without moving out, uploading or copying these data. In addition, federated analyses are performed on fully anonymized data, and only provide aggregated results (no individual finding)

Results

Eleven EpiCARE sites reported in the recent survey that they keep a database of healthy adults, and eight were open to the possibility to share their data. Fifteen

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centers reported that they keep some form of imaging database of their epilepsy patients. Data will be anonymized on site and added to a database with ability to filter data based on various parameters (age, sex, field strength, sequence, type of epilepsy). This database will be shared within the network. As a first step, only references to data will be available and we will have to ask individual centers' representatives when access of their neuroimaging data is wanted. A possible CPMS expansion to an online IT platform to store cohorts of healthy control imaging data, or that of specific epilepsy populations from individual centers, was also discussed with the IT project manager of the European Commission.

During the expert group meeting in February 2019, we further discussed the methodological and ethical issues of a centralized database of scans. It seems likely that the CPMS allows only uploading of patients' scans. We have asked the ERN IT platform whether collection and chronic storage of patient and control scans is possible. This is probably not the case. We discussed extensively the aspects of constructing healthy control templates, in order to perform MAP (morphometry analysis program) to post-process MRI's of individual patients with MRI-negative suspected FCD. In summary:

- we questioned whether it would be possible to merge control templates from different centers; in that case individual scans could stay in each center, only sharing templates (with no ethics / consent problems). Probably this is not an option.
- ideally control scans are stored centrally, and each time that MAP wants to compare a patient scan, a specific control template is constructed, based on available scans that are age-, MRI-system, gender-, and field strength – matched. In that case we need to collect scans on the E-PICARE IT platform, on which MAP will run in CURRY8
- even though we can thoroughly pseudonomize scans (deskull, deskin etc.) there will still be a code that links the scans with individuals. This is the reason some centers require specific consent for international storage/data sharing, and local consent is not sufficient.
- we discussed the trade-off issue between 1) larger number of scans (pooling MRI's of different scanners and different field strengths), and 2) higher specificity (scan/field-strength-specific MRI controls), when constructing control templates
- probably, as the best option to collect more healthy control data, we could download freely available MRI data for which ethics and consent issues have been taken care of, e.g. https://github.com/cMadan/openMorph/blob/master/README.md.

Part of the deliverable has been successfully achieved (register of consortium centers' neuroimaging databases in controls and epilepsy patients, inventory of and discussion about methodological and ethics issues regarding healthy volunteer MRI data collection and centralized storage, and of alternative methods to have control brain imaging data available).

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A) Other activities of the Work Package

1) We are currently optimizing the newly-developed MAP software, to be implemented as part of CURRY8, for centralized MRI post-processing availability for the network centers. Optimization is done with 40 UMCU FCD patients, comparing results with MAP07 and MAP18. In the future the new software will be validated.
2) An important other aim of WP3 is to establish a: “second opinion pathway for imaging review established”. The CPMS enables the re-review of patient’s images online, by expert radiologist, member of WP3 expert group. During our imaging expert meeting in Febr 2019, we agreed and decided that:
    - each expert radiologist should have access to CPMS
    - CPMS training sessions will soon be organized
    - the CPMS image-viewer system has been testes,some modifications have been requested and have now been implemented. Next, our neuroimaging radiology experts should approve that it is of sufficient quality and has all the features necessary to review.
    - physicians can upload a patient’s scan, in the form of a panel in CPMS. To do so, the standard ERN consent form has to be signed by the patient
    - radiologists who have access to CPMS can view the scans, but cannot download scans to be reviewed on their own viewer system
    - we agreed that the team of radiologists will circulate, with two to three being “on call” for one month. Once a scan is uploaded, the CPMS system will send a notification to radiology experts and other EpiCARE members. Each radiologist interested can comment on the scans, but the persons on call should at least give their comments within a reasonable time frame (say 1-2 weeks).

5 Conclusions

The results achieved are in accordance with most of the objectives for Worp Package 3 (neuroimaging), as detailed above.

6 Bibliography / References

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