CHAPTER 1

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Introduction

Diagnostic research

With the rapidly progressing technical developments in medicine during the last decades, more and more diagnostic tools have become available to clinicians. As a consequence, diagnostic decision-making in clinical practice has become more complex.[1-7]

Research is necessary to determine the role and usefulness of each diagnostic test in clinical practice.[1;2] While in the past diagnostic research used to focus on a single test under study, in clinical practice a diagnosis or decision is rarely based on information provided by a single diagnostic test. Therefore, the clinical value of a diagnostic test should be assessed in the context of the results of other diagnostic tests, which requires a multivariable approach.[3-7] By using a multivariable approach in diagnostic studies, it is possible to determine whether a particular test independently (i.e., beyond other, existing tests) contributes to the diagnostic process and whether the same diagnosis can be made with fewer tests without a decrease in the diagnostic accuracy of process.[3-7]

In diagnostic research, ideally the 'true' presence or absence of the disease under study is established in study patients with the same reference test or 'gold' standard.[2;8;9] However, such a reference test is not available for all diseases or the available reference test is such an invasive test with potential complications that its use in all study patients would be unethical.[6;10] In these research situations, an alternative is to use a consensus diagnosis established by a panel of experts as reference (either or not combined with clinical follow-up).[2;8;9;11]

Temporal lobe epilepsy surgery

The decision to perform resective surgery in patients with drug-resistant temporal lobe epilepsy is based on a complex diagnostic work-up. There is not a single reference test to determine eligibility for surgery that is appropriate for all potential surgical candidates. Surgery, with resection of the part of the brain that causes epilepsy, is a valid treatment option for a subgroup of patients with focal temporal lobe epilepsy refractory to medication.[12;13] Although postsurgical results

are excellent (70% of patients become seizure free, and in 95% a worthwhile reduction of seizures is achieved),[13;14] it is stated that surgery is underutilized worldwide.[15] Generally, the presurgical work-up to decide whether or not a patient is a candidate for surgery involves a series of consecutively performed diagnostic tests resulting in a final diagnosis or a final decision regarding eligibility for temporal lobe epilepsy surgery.[16;17] In the Netherlands, all potential surgical candidates undergo the same consecutive diagnostic work-up in a national program. A multidisciplinary team determines – after each consecutive test result is obtained – whether a final diagnosis or decision regarding eligibility can be made or whether additional tests are still required, using a consensus method. This multidisciplinary team consists of experienced epileptologists, (child) neurologists, clinical neurophysiologists, neurosurgeons, neuropsychologists, and neuroradiologists.[17] Consecutive diagnostic test results and all decisions made during the diagnostic work-up are recorded in a database. Over a period of about 30 years this has resulted in a rich source of information for a large cohort of patients that is available for research purposes.

This thesis describes the analysis of this cohort of patients referred for presurgical evaluation for temporal lobe epilepsy surgery. The main aims were to quantify to what extent certain diagnostic tests or consecutive steps in the presurgical diagnostic work-up truly contribute to the decision to proceed, or not, with temporal lobe epilepsy surgery. This posed two challenges. The first was to quantify each test or step of the diagnostic work-up. To achieve this, a panel of clinical neurophysiologists, experienced in the field of epilepsy, evaluated all potentially performed diagnostic tests (ranging from patient history to highly invasive intracranial EEG monitoring) and developed a long list of test results that could contribute to the decision to perform surgery in patients with temporal lobe epilepsy. The members of the multidisciplinary team, who are responsible for all decisions concerning epilepsy surgery in the Netherlands, provided input for the

development of this list. Then, every predefined test result was checked for uniformity of coding and interpretation, using kappa analysis between scoring researchers.[18;19]

The second challenge was the absence of one single adequate reference test that was performed in all patients to ultimately set the true decision for or against surgery. Intracranial EEG monitoring could be seen as the reference test for this situation. However, because this is such an invasive procedure (electrodes are placed intracranially directly on the brain or even in the brain tissue and only a small percentage of patients (4%) generally undergo this procedure), it would be unethical to perform this test in all patients entering the presurgical work-up. On the other hand, including the data of only those patients that indeed underwent intracranial monitoring would lead to biased results. [1;2;20-22] For these reasons, we used the final consensus diagnosis established by the multidisciplinary team, a diagnosis that was available for all patients in the cohort.

Outline of the thesis

Chapter two provides a systematic review of the literature on the presurgical work-up or diagnostic decision-making process for temporal lobe epilepsy surgery.

In chapters three to five, we assessed the independent contribution of different diagnostic tests used in the presurgical work-up to the diagnosis or decision whether to perform temporal lobe epilepsy surgery. Chapter three describes the contribution of basic non-invasive tests (patient history, routine EEG, MRI, and video EEG monitoring) to the decision regarding eligibility for surgery.

In chapter four, we describe the added value of positron emission tomography (FDG-PET), additional to that of non-invasive tests, to the decision whether to perform temporal lobe epilepsy surgery.

In chapter five, we focus on the intracarotid amobarbital procedure (Wada test), which is performed to assess language lateralization and the risk of

development of postsurgical global amnesia. We assessed the added value of a contralateral injection during the Wada test, compared to an ipsilateral injection only, regarding the decision to perform surgery.

In chapter six, we focus on the prediction of seizure freedom one year after surgery in patients who underwent temporal lobe epilepsy surgery, based on a multivariable model including all known potential predictors for post-surgical seizure freedom.

In chapter seven, we discuss the magnitude of, and reasons for, underutilization of epilepsy surgery in the Netherlands.

Lastly, in chapter 8, we discuss our findings and give recommendations for future research.