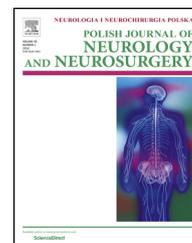


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Original research article

Diffusion tensor tractography imaging in pediatric epilepsy – A systematic review



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ABSTRACT

Purpose: Recent years brought several experimental and clinical reports applying diffusion tensor tractography imaging (DTI) of the brain in epilepsy. This study was aimed to evaluate current evidence for adding the DTI sequence to the standard diagnostic magnetic resonance imaging (MRI) protocol in pediatric epilepsy.

Material and methods: Rapid and qualitative systematic review (RAE, Rapid Evidence Assessment), aggregating relevant studies from the recent 7 years. The PubMed database was hand searched for records containing terms “tractography AND epilepsy.” Only studies referring to children were included; studies were rated using “final quality of evidence.”

Results: Out of 144 screened records, relevant 101 were aggregated and reviewed. The synthesis was based on 73 studies. Case-control clinical studies were the majority of the material and comprised 43.8% of the material. Low ‘confirmability’ and low ‘applicability’ referred to 18 and 17 articles (29.5% and 27.9%), respectively. The sufficient quality of evidence supported performing DTI in temporal lobe epilepsy, malformations of cortical development and prior to a neurosurgery of epilepsy.

Conclusions: The qualitative RAE provides an interim estimate of the clinical relevance of quickly developing diagnostic methods. Based on the critical appraisal of current knowledge, adding the DTI sequence to the standard MRI protocol may be clinically beneficial in selected patient groups with childhood temporal lobe epilepsy or as a part of planning for an epilepsy surgery.

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1. Introduction

Diffusion tensor imaging (DTI) is one of the magnetic resonance imaging (MRI) sequences that visualizes white matter bundles. Physiologically, the diffusion of water molecules in the brain is restricted to the long axis of the white matter. Parameters such as the direction of the diffusion of a single voxel can be defined thanks to the magnetic gradient set by the DTI sequence [1]. The obtained mathematical model is processed into maps of apparent diffusion coefficient (ADC), fractional anisotropy (FA) or mean diffusivity (MD). A three-dimensional model of individual white matter pathways is built by combining voxels aimed in a particular direction [1,2]. The analysis of all the connections between all areas of white matter produces a connectome (a whole brain connectivity map). It is noteworthy that DTI is a non-invasive method and does not generate additional costs. Many authors described white matter changes occurring in various epilepsy syndromes. However, there are neither guidelines nor any systematic reviews which objectively assess the clinical benefit of DTI in pediatric epilepsy. The existing literature presents scattered data limited to specific diagnoses, small patient samples and are often case-control studies with biased matching method [2-4].

The aim of this study is to qualitatively assess the existing evidence about the use of DTI in diagnosing pediatric epilepsy. The main research question: is it justified to add the DTI sequence to the standard MRI protocol to diagnose pediatric epilepsy?

2. Material and methods

After reaching consensus regarding the methodology, the authors designed the study protocol and divided the tasks. Rapid Evidence Assessment (RAE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [5,6] methods were chosen. Three authors identified, screened and included full-text articles as well as synthesized the data. The PubMed (Medline) database was searched using the phrase "tractography" AND "epilepsy," restricted to the last 7 years. Included articles were cross-referenced and duplicates were removed using the Mendeley software (version 1.12.1, Mendeley, Inc., New York). Screening was based on titles and abstracts. Original articles, review articles, expert opinion and lab animal research reports were included. Only articles regarding the pediatric population and pediatric-type epilepsies were included (i.e. post-stroke or alcohol-induced epilepsy were excluded). The raw data were compiled; the quality of evidence of each study was assessed using the criteria set by Cesario [7] (Table 1).

Statistical analysis was performed using GraphPad Prism v.6.05 (GraphPad Company, La Jolla, CA).

3. Results

The initial search yielded 126 records. Additional 39 records were found during the identification stage. After removing the duplicates, 144 articles were screened. At this stage 22 articles

Table 1 – Abbreviated instructions for qualitative assessment of scientific papers. In addition to the final mark (Q1-Q3), the papers were rated in terms of confirmability and applicability as key determinants of adding the tractography sequence to routine clinical practice. Adapted from Cesario and Santa-Donato [7].

Read the study and score each of the CATEGORIES.

Use the quality rating SCALE of 0-3.

Assess the FINAL QUALITY OF EVIDENCE.

CATEGORIES:

1. Descriptive vividness
2. Methodological congruence:
 - a. Rigor in documentation
 - b. Procedural rigor
 - c. Ethical rigor
 - d. Confirmability
3. Analytical precision
4. Theoretical connectedness
5. Heuristic relevance
 - a. Intuitive recognition
 - b. Relationship to existing body of knowledge
 - c. Applicability

SCORING SCALE:

3 = "good" = 75-100% criteria met

2 = "fair" = 50-74% criteria met

1 = "poor" = 25-49% criteria met

0 = "no evidence that the criteria is met" = 0-24% criteria met

FINAL QUALITY OF EVIDENCE RATING:

Based on the total scores for each of the five categories described above (1-5).

Q1: total score of 23-30

Q2: total score of 15-22

Q3: total score of 0-15.

were excluded based on their titles and abstracts. In the eligibility stage, articles were assessed based on their full text. Finally, 101 articles were included in the synthesis (Fig. 1).

Of all the included articles, only 73 contained clinically useful information about pediatric epilepsy and were included in the analysis. A slight majority of the included studies were case-control studies ($n = 32$; 43.8%), followed by case series ($n = 23$, 31.5%), 11 review articles and 1 systematic review. There were no randomized clinical trials on this subject. Nearly half of the included articles were published in the US or UK ($n = 33$; 43.8%). The most frequent types of epilepsy noted in the analyzed literature were temporal lobe epilepsy (TLE) and mesial temporal lobe epilepsy (MTLE) ($n = 22$; 30.1%).

Of the 61 original articles assessed for quality, 21 (34.4%) were rated as Q1 and 20 (32.8%) each as Q2 and Q3. The mean and median quality scores in our sample were 60.7% (SD \pm 20.6%) and 63%, respectively. The analysis of the individual Q ratings indicated that a relatively small number of articles were scored as having low confirmability (0 or 1 points; 18 articles (29.5%)) or low applicability (0 or 1 points; 17 articles (27.9%)). The quality of articles regarding TLE and MTLE was compared with the quality of articles about other types of epilepsy. The Q ratings and its individual components (e.g. confirmability and applicability) were similar. Specifically, the papers about TLE and MTLE had a non-significantly higher confirmability and applicability and a non-significantly lower final quality of evidence rating (Q) ($p = 0.15-0.58$) (Fig. 2B).

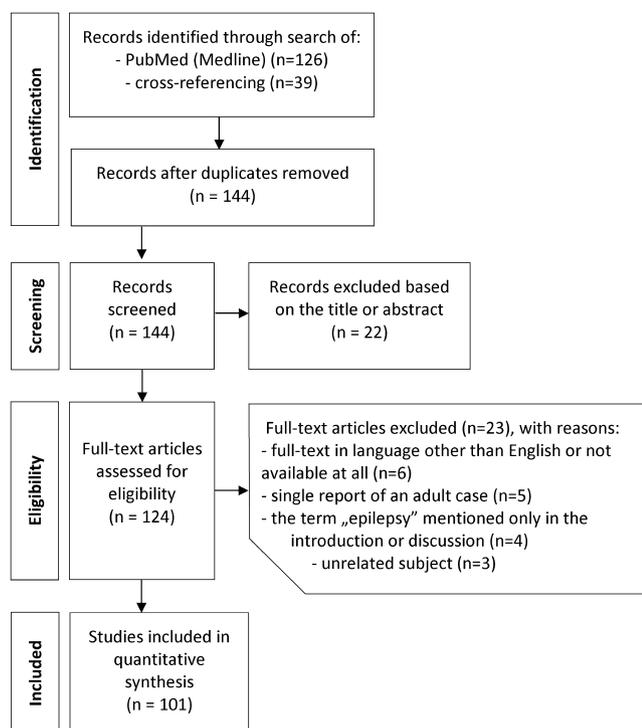


Fig. 1 – Flowchart demonstrating the phases of this systematic review [5].

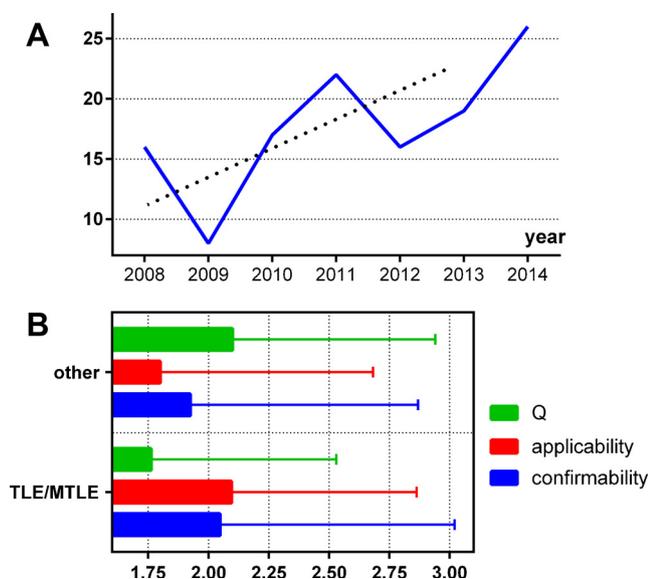


Fig. 2 – (A) Number of papers about use of tractography in epilepsy published in a given year (blue line). Dotted line indicates estimated linear increase in time. (B) Quality estimates of papers regarding temporal lobe epilepsy (TLE) or mesial temporal lobe epilepsy (MTLE) versus other epilepsies. (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

Based on our analysis, adding the DTI sequence to the MRI protocol seems to be most beneficial for patients with TLE. Speech function of patients with TLE revealed arcuate fasciculus degeneration and reorganization of speech pathways in the contralateral side of the brain [2,8–10]. Lower fractional anisotropy (FA) together with higher apparent diffusion coefficient (ADC) correlated with the duration of epilepsy [11–13]. Therefore, measuring these parameters of anisotropy and diffusion may have diagnostic or prognostic value [14].

A total of 6 case-control studies focused on MTLE patients [15–20]. In this patient group, DTI allowed visualization of changes in the fornix, cingulate gyrus, precuneus and decreased connections in the hippocampus. Whereas the obtained connectome revealed a reduced global effectiveness of white matter fibers and reorganization of the limbic system pathways. However, based on the currently available knowledge DTI does not have diagnostic value in the MTLE patient group and the results of this scan will not alter the therapeutic management. Therefore, DTI in the MTLE patient group is disease research purposes only.

The use of DTI in patients with malformations of cortical development (MDC) is at this point demonstrated on a just 41 patients [21–26]. Despite such small sample size, DTI allowed visualization of white matter changes that were otherwise not visible in standard MRI protocols. The interesting new information these articles add to the existing knowledge requires clinical validation, particularly the combination of DTI with functional MRI and electroencephalography (EEG).

Much less has been published about other types of epilepsy. Scant evidence pointed to the diagnostic and/or therapeutic value of the DTI sequence in Congenital Bilateral Perisylvian Syndrome (arcuate fasciculus agenesis) and juvenile myoclonic epilepsy (motor and premotor cortex). Decreased FA value correlated with lower neuropsychological test scores. FA value was also related with disconnection syndrome, influenced diagnosing alexia, and facilitated monitoring the progression of white matter changes.

The conclusions of 5 review articles did not equivocally indicate in which types of epilepsy is DTI diagnostically or therapeutically beneficial. These narrative overviews were not designed in a systematic review fashion and their authors did not intend to appraise the utility of DTI in epilepsy.

A separate subset of the articles was devoted to the preoperative use of DTI in epilepsy (18 articles of 73; 24.7%). The mean quality of evidence (Q), mean confirmability and mean applicability of these articles did not differ from the rest of the sample ($p = 0.11-0.94$). According to the results, DTI is an important element of preoperative visualization of the optic radiation, motor areas, optic cortex, other eloquent areas, as well as plays a role in the planning of the resection of the epileptiform brain changes. The benefits of DTI in preoperative diagnostics are also confirmed by 4 review articles and one systematic review.

4. Discussion

The diffusion-weighted imaging is the method of qualitative and quantitative imaging of the white matter [2]. The introduction of diffusion tensor in 1994, the definition of FA

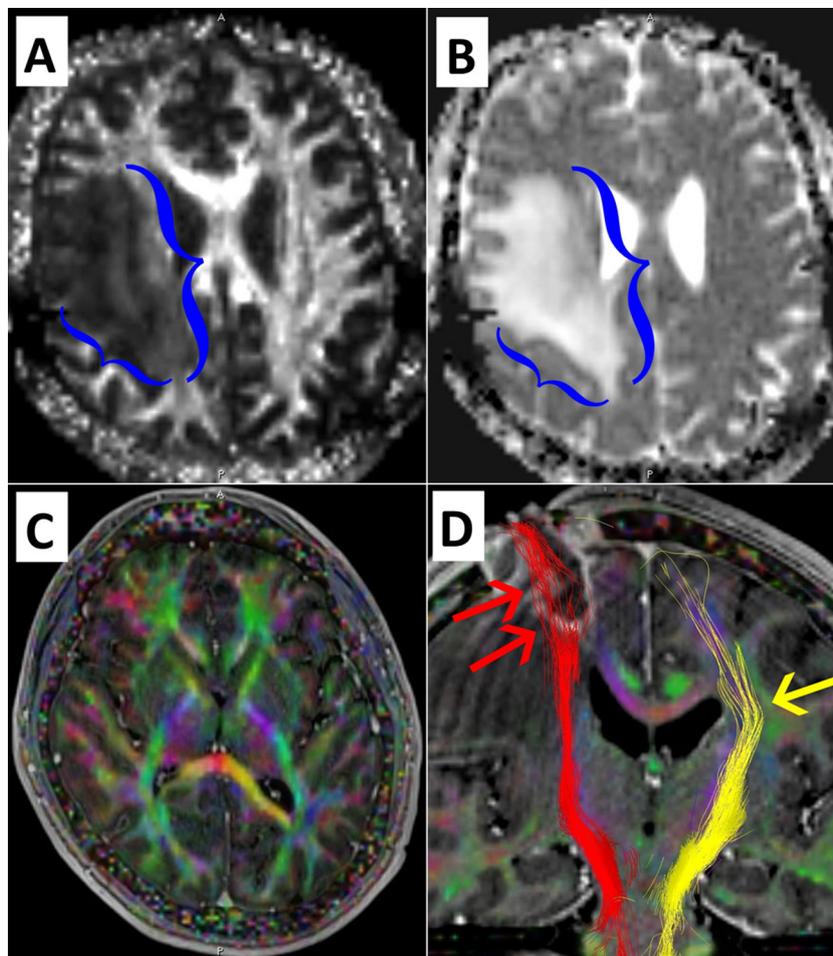


Fig. 3 – Magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) of a patient with partial seizures after resection of cerebral abscess. (A) Fractional anisotropy sequence. (B) A sequence with average mean diffusivity. The blue brackets mark the edematous area with low anisotropy (A) and high diffusion (B) compared to the rest of white matter. (C) Fusion of T1-dependent image and the sequence of the directionally encoded colors of fibers. The red arrow points to the artifact of pseudo-penetration of the abscess remnant by the tractography fibers. The yellow arrow points to a part of the corona radiata which was not pictured using tractography. This diagnostic error is due to an imperfect algorithm which assumes only one possible direction of anisotropy. (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

two years later, followed by the mapping of the white matter pathways and building the connectome caused an exponential increase in the use of DTI in neurosurgery, neurology and psychiatry [1,3,27]. Changes of DTI-derived values include FA, mean anisotropy, MD and altered course of white matter fibers (Fig. 3).

The mean final quality of evidence ratings (Q), confirmability and applicability of TLE or MTLE articles did not differ from the means of articles regarding other epilepsy types. Despite that, the qualitative assessment of these articles' conclusions suggests that adding DTI to the standard MRI protocol might be justified. DTI might act as a supplementary method of speech examination [9,10,12,28], a noninvasive marker of the progression of the white matter changes [27,29] or provide new information about the reorganization of nerve fiber connections.

Another subset of patients who can benefit from DTI are those who are referred for neurosurgical procedure. Thanks to the compatibility of the saved MR images (DICOM format),

tractography may be used at any stage of the procedure, including the assessment of nerve pathway damage. There is a high risk of visual pathway (Meyer loop) damage during partial temporal lobectomy as well as during selective amygdalohippocampectomy [30,31].

It appears to be worthwhile to perform the DTI sequence for disease research and experimental purposes in centers with a designated research team. In our systematic review, 32 of 73 (43.8%) studies were case-control design and matching healthy subjects. In addition to these studies, prospective collecting of patients with DTI should be supported, even without a previously established research goal. The MD and ADC values decrease directly following an epileptic attack, however these changes do not occur in all patients [2]. Due to logistic reasons, performing MRI scans shortly after an epileptic attack might be possible only in selected centers. At this point, the methods of DT image acquisition, processing and interpretation are not perfect. Among the factors influencing the results are: the

variety and precision of mathematical algorithms, anatomic variants, cerebral edema, nerve fiber degeneration, inflammation, compression and infiltration by tumors [1,2,32]. The subjective radiological assessment of the white matter topology and fibers is another imperfection of the DTI. Depending on the neural tract, the interobserver agreement might be insufficient ($Kappa = 0.6–1.0$) [32,33]. In the case of connectomes, the results depend not on the observed but instead on the limitations of the automatic imaging of cerebral hemispheres [34]. The various methods used at various radiology centers limit the value of review articles that summarize single-studies results [32]. That is why our systematic review analyzes only the quality of evidence, confirmability and applicability of existing articles. It seems that translation of the methods and interpretation experience from one epilepsy diagnostic center to another is not possible. Given the challenges with interpreting MRI scans, it is prudent to include neurosurgeons and/or radiologists experienced with DTI in the epilepsy diagnostic team.

Patient safety is the priority during MRI examinations and adding the DTI sequence to the standard protocol does not increase any risk to the patient. There are no known studies evaluating the costs vs. benefits of DTI in patients with epilepsy. The DTI sequence may take from 2 to 15 min to complete, depending on the scanner and/or the number of encoded directions. Based on our Rapid Evidence Assessment, adding the DTI sequence may be clinically beneficial to patients with TLE or during the planning of epilepsy surgery.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.pjnns.2015.10.003>.

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