Diagnostic Value of Fractional Anisotropy in Detecting Hippocampal Sclerosis: A Study on Intractable Mesial Temporal Lobe Epilepsy with Normal MRI

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ABSTRACT

Purpose: This study aimed to investigate whether Fractional Anisotropy (FA) is reliable in detecting hippocampal sclerosis on intractable Mesial Temporal Lobe Epilepsy (MTLE) with normal MRI as measured from the degree of of neuronal loss, gliosis and axonal sprouting. **Method:** Twenty-three MTLE patients underwent surgery and 10 healthy volunteers were involved in this study. The MTLE diagnosis was based on semiology and ictal EEG, while hippocampal sclerosis was diagnosed using standardized MRI, followed by DTI FA. Histopathological analysis of hippocampus was performed with NeuN, GFAP, and NPY staining to detect the neuronal loss, gliosis, and axonal sprouting. Correlation and Diagnostic test was done to asses of diagnostic value FA. **Result:** Ten MTLE patients showed normal MR, 4 with hippocampal sclerosis and 6 were with FCD. The value of FA was significantly lower compared with healthy subject. The cut-off point of FA in detecting hippocampal sclerosis was 0.17 (AUC=0.89). The sensitiviy, specificity, positive predictive value, and negative predictive value of FA were 81.8%, 72.3%, 64.3%, and 89.56% respectively. There was significantly correlation between FA with the degrees of neuronal loss and gliosis. The concurrence between FA with EEG 7 out of 10 patients. **Conclusion:** Fractional Anisotropy has a good diagnostic value in detecting hippocampal sclerosis on normal MRI patients. In addition, this technique also shows a moderate association with degrees of neuronal loss and gliosis.

Keywords: *intractable MTLE; normal MRI; DTI; fractional anisotropy; hippocampal sclerosis.*Mesial

Temporal Lobe Epilepsy (MTLE) is one type of epilepsy appeared in adults that most often turns into intractable epilepsy. Hippocampal sclerosis is the most common cause of intractable MTLE. In this case, surgery will give a more satisfying result [1-3]. Surgery therapy needs diagnosis precision in determining the location as well as lateralization of epileptogenic zone in order to achieve a better surgery result. High Tesla MRI is a noninvasive examination has an excellence anatomic resolution and sensitive in detecting microstructural lesions, has sensitivity about 85-100% [4]. However, in about 20-30% intractable focal epilepsy patients undetected using standardized MRI [5].

Advanced Diffusion Tensor Imaging (DTI) -MRI technique can visualize a complex brain's tissue structure [6]. MD and ADC of DTI correspond to diffusivity whereas FA corresponds to anisotropy. Previous studies indicates a significant increase of mean diffusivity and a decrease of FA on ipsilateral hippocampal formation compared with the contralateral side, and also when compared with healthy subjects [7]. DTI role in visualizing a larger cerebral network, including extra temporal involvement in epilepsy with

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hippocampal sclerosis, which marked by the increase of diffusivity on epileptic hippocampal and ipsilateral temporal structure followed by the decrease of anisotropy along the temporal lobe. A decrease of diffusivity on hippocampal sclerosis, amigdala and contralateral temporal pole as well as an anisotropy decrease on ipsilateral posterior extra temporal region [8]. An MTLE study with hippocampal sclerosis shows that there is a correlation between histopathology and in vivo DTI i.e. an increase of extra axonal fraction and a cumulative decrease on both axon membrane circumference and myelin area at fornix fimbria [9]. There is an increase of FA along with the increase density of axonal mossy fiber sprouting on histopathology analysis using Timm staining [10]. There are no available data yet on the correlation between FA and axonal mossy fiber sprouting histopathology on humans.

There are only a few researches that study the use of DTI on epilepsy patients with normal MR and the results were inconsistent. Previous study finds diffusion abnormality on only 27% patients (8 out of 30 patients) with partial seizure cryptogenic [10]. In this research 6 out of 8 patients with diffusion abnormality and increase in diffusion correlate with epileptiform abnormality. Another study finds 64.3% (9 out of 14 patients) with diffusion change that is consistent with its intracranial EEG [8]. There is a significant increase in MD on 13 out of 15 subjects, an increase on FA (2 out of 15), and a decrease on FA (5 out of 15). In this study, the diffusion change is compared with healthy subject controls [8]. The changes of DTI (MD and FA) parameter can show a change in and around hippocampal and also on normal MRI epilepsy [12]. There has been no research concerning DTI diagnostic test on MRI-normal MTLE patients with histopathological analysis as a gold standard. Therefore, this study aimed to investigate whether Fractional Anisotropy (FA) is reliable in detecting hippocampal sclerosis on intractable Mesial Temporal Lobe Epilepsy (MTLE) with normal MR as measured from the degree of neuronal loss, gliosis and axonal sprouting.

MATERIAL AND METHODS

Patients

Twenty-three MTLE patients and ten healthy subjects were involved in this study. The criteria for healthy subject were who do not have any history of neurological and psychiatric disorder and have normal conventional MRI. The mesial temporal lobe epilepsy diagnosed according on ILAE criteria: 1) semiologically consistent with MTLE, included: epigastric, autonomic, or psychic auras followed by behavioral arrest, progressive clouding of consciousness, oroalimentary and manual automatisms, and autonomic phenomena; 2) unilateral or bilateral anterior, and temporal mesial of interictal spikes; 3) electroencephalogram video monitoring with seizure onset especially from temporal lobe; 4) an intractable TLE defined as response failure of 2 antiepileptic drug (AED). All MTLE subjects meet the following inclusion criteria: age $\geq$ 7 years; able to fulfill MRI examination requirements; and able to provide hippocampal surgery specimen for histopathological analysis. Drop out criteria when the surgery's specimen cannot be analyzed histopathologically.

Magnetic Resonance Imaging

All subjects were scanned on 1,5T MR scanner (Signa HDxt 16 Ch, GE Milwaukee USA) at Department of Radiology dr. Kariadi General Hospital and St. Elisabeth Hospital, Semarang Indonesia.
MRI epilepsy standard conducted on MTLE were T1, T2, FLAIR (Fluid Attenuation Inversion Recovery) sequence which perpendicular with hippocampal axis.

DTI

DTI were acquired using a single-shot echoplanar diffusion weighted (SE-EPI) applied simultaneously along 6 directions (b= 1000 s/mm2) as well as an acquisition without diffusion weighted (b=0 s/mm2). Moreover 30 contiguous axial slices were acquired with a 3 mm slice thickness with no gap. The acquisition parameters were: repetition time (TR):6100ms, echo time (TE):106 ms, number of excitation (NEX)= 2, flip angle 900, matrix 128x128, FOV (field of view) 230x230 mm. The total acquisition time was 4,5 min. All scans were reviewed by an experienced radiologist.

Image analysis

Data were transferred to independent workstation to measure FA and MD. FA and MD were calculated with available software application provided by manufacturer. Region of interest (ROI= 20-30 mm2) were selected on the axial section from a small oval region drawn in 4 locations (2 at head, 1 at body and at tail of hippocampus) then calculating the average. Adjacent cerebrospinal fluid-containing pixels were avoided in ROIs to reduce the partial volume effects. (Figure 1)

Histopathological staining

Haematoxyllin-Eosin (HE), NeuN, GFAP and Neuropeptide Y (Biocare) staining are to analyze the neuronal loss (NeuN), gliosis (GFAP) and axonal/Mossy Fiber sprouting (Neuropeptide Y). The score of lesion was categorized as mild grade when < 70% neuronal loss and there is no intensely stained for gliosis or axonal sprouting. Lesion score criteria categorized as severe grade when > 70% neuronal loss and intensely stained for gliosis or axonal sprouting.

Ethic
This study was approved by the local ethics committee. Informed written consent to participate in the study was also obtained from the patients and healthy volunteers.

Statistical analysis
Accuracy FA, in detecting hippocampal sclerosis, included sensitivity, specificity, positive predictive value, negative predictive value, and the association between FA with neuronal loss, gliosis and axonal sprouting.

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RESULTS

Clinical characteristics
The mean of MTLE group age was 24 years, the youngest was 14 years and the oldest was 41 years. Age mean in the healthy volunteer group was 31 years (ranging from 26 to 36 years). The age of healthy volunteer group showed no significant difference (p=0.19). In MTLE group 12 subjects were females (52.17%) and 11 were males (47.83%). As in healthy volunteer group most subjects were females (70%). The average duration of illness was 12.9 years ranging from 2 to 32 years. The average age of onset was 11.1, with onset range from 1 year to 22 years. Table 1, 2 and 3, showed data for patient group and the healthy control subject, along with the relevant medical history and DTI measurement

EEG and standardized MRI T2
The details of EEG lateralization were as follows: right 8, left 12, normal 2, and undetermined 1. Next, EEG video monitoring and intracranial were carried out towards 2 normal and 1 undetermined of EEG. From here it was found that there were 10 right and 13 left EEG lateralization. (Table 1)Based on T2/FLAIR parameter on 23 MTLE subjects, it was found that 11 hippocampal sclerosis (43.48%), 1

dysplasia, and 1 heterotopy. MRI T2/FLAIR right lateralization was 4 subjects, 5 with left lateralization, 10 subjects were normal, 1 subject bilateral, and 2 subjects' lateralization to the right (dysplasia and heterotophy). On 10 TLE cases with normal MRI, lateralization of 9 patients was determined by EEG monitoring and 1 case intracranial EEG. Furthermore, the location of lesion was identified by PET examination.

Table 1. Clinical characteristics of subjects and histopathological findings

Patient/ Sex/ Age (Y)	Age at onset (Y)	Duration of illness (Y)	Scalp EEG	Video EEG	Surgery	Histopathological Finding
1/ F/ 25	8	17	Lt		Lt SAH	Hippocampal sclerosis
2/M/30	18	12	Rt		Rt ATL	Hippocampal sclerosis
3/ F/19	9	10	N	Lt	Lt SAH	Hippocampal sclerosis
4/ M/26	5	21	Lt		Lt SAH	Hippocampal sclerosis
5/ F/28	22	6	Lt		Lt SAH	Hippocampal sclerosis
6/ F/17	1	16	Lt		Lt ATL	Hippocampal sclerosis
7/ M/17	12	5	N	Rt	Rt ATL	Hippocampal sclerosis
8/F/24	22	2	Lt		Lt SAH	Hippocampal sclerosis
9/ F/20	6	14	Lt		Lt ATL	Hippocampal sclerosis
10/ M/24	12	12	Rt	Lt	Lt ATL	Hippocampal sclerosis
11/ F/40	20	20	Lt		Lt SAH	Hippocampal sclerosis
12/ M/14	9	5	Rt		RT ATL	Focal Cortical Dysplasia
13/ M/41	15	26	Rt		Rt ATL	Focal Cortical Dysplasia
14/ F/34	9	25	Rt		Rt ATL	Focal Cortical Dysplasia
15/ M/18	16	2	Rt		Rt ATL	Focal Cortical Dysplasia
16/ M/16	5	11	Lt		Lt SAH	Focal Cortical Dysplasia
17/M/24	4	20	N	Rt	Rt ALT	Focal Cortical Dysplasia
18/ M/17	14	3	Rt		Rt ATL	Focal Cortical Dysplasia
19/F/20	7	13	Rt		Rt ATL	Focal Cortical Dysplasia
20/F/22	12	10	Lt		Lt SAH	Focal Cortical Dysplasia
21/ M/37	5	32	Lt		Lt SAH	Focal Cortical Dysplasia
22/F/20	15	5	Rt		Rt ATL	Focal Cortical Dysplasia
23/F/19	10	9	Lt		Lt SAH	Focal Cortical Dysplasia

MRI DTI FA analysis

FA on FCD and hippocampal sclerosis group were significantly lower compared to the normal subject group. There were a significant difference between FA values in hippocampal sclerosis group and FCD compare control group. (Table 4) However, there was no difference found between hippocampal sclerosis group and FCD. On MTLE with normal MRI, the FA showed a compatible lateralization compared to EEG (7/10).

Histopathological analysis

A complete structure of hippocampal was not found in all samples, however an enthorinal cortex structure, subiculum and CA1 were found. Neuronal loss and gliosis were prominent on CA1 of all subjects (probably hippocampal sclerosis). Based on the histopathological analysis of the surgery result, there were 11 subjects with hippocampal sclerosis and 12 with Focal Cortical Dysplasia (FCD).

MTLE with normal MRI on 10 subjects, 4 (40%) was considered as hippocampal sclerosis, with the following level of immunohistochemistry examination: 1 subject with mild gliosis, 50% neuronal loss, severe axonal sprouting, 1 subject with mild gliosis, 70% neuronal loss, mild axonal sprouting, 2 subjects with severe gliosis, 80% neuronal loss, severe axonal sprouting. Meanwhile, 6 subjects (60%) were histopathologically showed FCD. In 6 FCD, 4 subjects showed hyperintensity of hippocampal.

The diagnostic value of FA

A diagnostic test was conducted based on the result of COP FA. AUC of ≥ 0.7 was considered suitable for an analysis. In this study the size of AUC FA was 0.89, with cutoff point (COP) = 0.17. The sensitivity, specificity, positive predictive value, and negative predictive value of FA were 81.8%, 72.3%, 64.3%, and 89.56% respectively (Table 5). There were significantly negative correlation between FA with degree of neuronal loss ($r = -0.557$; $P = 0.006$) and gliosis ($r = -0.438$; $P = 0.037$ Spearman test).

Table 2. Summary of subject population evaluated with DTI

Patient/ Sex/ Age (Y)	MR T2	FA		MD (x10-3)	
		L	R	L	R
1/ F/ 25	Lt	0.19	0.18	1.29	1.19
2/M/30	N	0.17	0.16	1.31	1.29
3/ F/19	N	0.13	0.16	1.44	1.25
4/ M/26	Lt	0.13	0.15	1.47	1.24
5/ F/28	N	0.17	0.19	1.09	1.2
6/ F/17	N	0.22	0.15	1.15	1.21
7/ M/17	Rt	0.17	0.14	1.09	1.29
8/F/24	Lt	0.17	0.15	1.36	1.33
9/ F/20	Lt	0.12	0.13	2.13	1.38
10/ M/24	Lt	0.12	0.26	1.44	1.27
11/ F/40	N	0.18	0.19	1.3	1.23
12/ M/14	Rt Displasia	0.20	0.23	1.22	1.31
13/ M/41	Rt Heterotopia	0.19	0.25	1.21	1.20
14/ F/34	Rt	0.20	0.17	1.39	1.23
15/ M/18	N	0.19	0.16	1.31	1.31
16/ M/16	Lt	0.20	0.19	1.22	1.26
17/M/24	Rt	0.15	0.16	1.22	1.30
18/ M/17	N	0.16	0.15	1.21	1.24
19/F/20	Rt	0.20	0.17	1.23	1.25
20/F/22	N	0.19	0.18	1.27	1.29
21/ M/37	N	0.16	0.16	1.23	1.22
22/F/20	N	0.21	0.19	1.26	1.38
23/F/19	N	0.18	0.17	1.31	1.37

DISCUSSION

In this study FA has a good diagnostic value in detecting hippocampal sclerosis. Besides, FA value in MTLE case with MRI negative is lower than the one in control group. It also shows 70% lateralization capability in accordance with EEG. It is different from the increase in MD which was caused by myelin damage, FA decrease was caused by axonal degeneration axonal degeneration, the decrease of FA correlates significantly with the perimeter of total axon in an area [9]. Axonal sprouting and synaps reorganization with neuronal loss is the characteristic of hippocampal sclerosis on dentate gyrus neuron. The decrease of CA 3 hippocampal pyramidal cell is related to the enlargement of axonal sprouting that can decrease the inhibition function of dentate gyrus. In a bigger scale, spreading also happens in white matter. The result of correlation test in this study also finds a moderate correlation among the degrees of neuronal loss, gliosis and axonal sprouting. A study using DTI on Wistar rat also indicates the increase of FA along with the increase of axonal mossy fiber sprouting density on histopathological analysis with Timm staining [10]. Arfanakis et al study shows a significant increase in radial diffusion and decrease of FA on internal capsule, as well as anterior and posterior corpus callosum. In his research, Rugg Gunn indicates that the decrease of FA and the increase of MD have lateralization capability on MTLE. A change of white matter happens in both MTLE patients with hippocampal sclerosis and those without hippocampal sclerosis.

Table 3. Summary of the healthy control evaluated with DTI

Control/ Sex/ Age (Y)	FA		MD (10-3)	
	L	R	L	R
1/ M/ 36	0.20	0.20	1,17	1,17
2/M/35	0.21	0.25	1,07	1,18
3/ F/26	0.22	0.23	1,07	1,20
4/ F/34	0.23	0.29	1,08	1,04
5/ F/26	0.22	0.24	1,16	1,18
6/ F/35	0.26	0.23	1,15	1,15
7/ F/29	0.22	0.26	1,21	1,18
8/M/33	0.25	0.24	1,11	1,13
9/ F/29	0.20	0.25	1,13	1,11
10/ F/30	0.23	0.23	1,20	1,20

The diffusion process of free water molecule in brain MRI is likely to measure the microstructure (restricted diffusion due to cross fiber, the large number of cells, demyelinization, or gliosis). Some factors also affect diffusion, such as fibre diameter and density, membrane permeability, and myelinization that can influence the direction and the size of the shift of water. FA is a water diffusion deviation index of spherical random movement. Meanwhile, MD is the scalar marker of diffusion size in each voxel. FA has a large spreading pattern, whereas MD anomaly has quite bigger restricted distribution [9, 15].

Table 4. FA MRI DTI of hippocampal sclerosis, FCD (histopathology) and healthy volunteers

		Mean (SD)	
Parameter FA	Hippocampal Sclerosis	FCDHealthy volunteers	P
Right	0.17 (0.03)	0.18 (0.03)0,24 (0.02).	0.001[a]
Left	0.16 (0.03)	0.18 (0.02)0.22 (0.02)	0.000[a]

Table 5. Diagnostic value of FA and MD to detect hippocampal sclerosis

MRI Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuration (%)
FA	81.8	72.3	64.3	89.5	78.8
MD	81.8	68.2	56.2	88.2	72.7

Normal MRI can be caused by unclear bilateral and unilateral atrophy as well as symmetrical hippocampal. The etiology of epilepsy is a complex process of interaction which involved genetic and environment factor which affects treatment plan and prognosis. In intractable epilepsy, surgery is still the main option. The process of intractable epilepsy surgery relied on the information of the location of the focal epileptogenic zone. Thus, MRI examination is a reliable method as an early screening to diagnose any structural defects regarding epileptogenic zone. A clearly measurable lesion is mesial temporal sclerosis (hippocampal sclerosis) which is the main cause of most MTLE cases.

Besides hippocampal sclerosis, intractable epilepsy can be caused by extratemporal epilepsy, which covers almost 30% of cases. MRI examination cannot identify this lesion (Non Lesional Neocortical Epilepsi/NLNE). NLNE caused by FCD is often undetected by regular MRI examination. Currently, pathology specimens are still unable to give a good surgery outcome compare to those who present a clear epilepsy lesion. Epilepsy cases with normal MRI examination needs multimodality treatment in order to determine the epileptogenic zone.

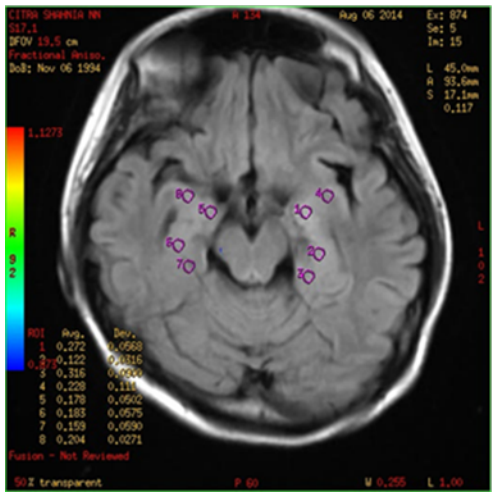

Fig.1 ROI's placement in hippocampal location

Qualitative MRI T2 examination which measured qualitatively is showed by hyperintense or non-hyperintense. Qualitative assessment is very subjective. Therefore, the ability to diagnose is not good enough, especially to T2 which able to be covered with LCS, especially on T2 that can be interfered with Liquor Cerebro-Spinal (LCS) hyperintense. In this case T2 is confirmed by FLAIR examination, which will show LCS as a hypodense so FLAIR can confirm in this examination, which will show LCS as a hypointense structure thus will look contrast if there is a hyperintense lesion in hippocampal.

The previous study shows a pathological finding on ELTI with normal MRI, i.e. 50% gliosis, microdisgenesis and cortical dysplasia are found [15]. The occurrence of FCD is due to the cortical malformation development, which is considered the most often cause of intractable MTLE in children and the second and third place in adults. The cause of intractable MTLE in adults is hippocampal sclerosis. A new classification shows a modification of Palmini classification [16]. FCD type 1 shows mild symptoms and slower onset usually occur in adult age and result in changes in temporal lobe. The second clinical symptom which is more severe is found in children. An extensive change is seen outside the temporal lobe with predilection of location in the frontal lobe. The third type of the new classification is the combination of either type 1 or 2 with other pathology, for example hippocampal sclerosis, tumor, vascular malformation or other pathology found during the early life phase [17]. MRI also able to show a clear pathology especially in FCD type 2. However, in type 1 pathology is often unclearly seen, and thus having a normal MRI examination.

CONCLUSIONS

The diagnostic value of FA MRI DTI in detecting of hippocampal sclerosis are 81.8%, sensitivity, 72.3% specificity, 64.3% positive predictive value and 89.5% negative predictive value respectively. Lateralization concordance between FA and EEG is 7 out of 10 patients with normal MRI. Therefore, FA shows a moderate significant association among neuronal loss, and gliosis.

No potential conflicts of interest relevant to this article were reported.

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