MR imaging of cerebellum volumetric analysis in epileptic patient

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Abstract

Purpose: To investigate the cerebellar volume change in epileptic patients. It's said that the prevalence of cerebellar atrophy in chronic focal epilepsy is about 30%. Cerebellar atrophy in epileptic patient was told to be due to the damage of seizure itself, drug intoxication and other factor related to epilepsy. The aim in this study is to 1.analyze the cerebellar volume difference between patient and control group. 2.the possible factors that cause cerebellar atrophy and it's significance

Methods: A retrospective, case-controlled cross-sectional study. We collected 15 epileptic patients from epileptic clinic and detail the history about seizure duration, drug history, epileptic syndrome, seizure type and epileptic focus. We also enrolled 19 healthy (10 male and 9 female) subjects from our neurological health examination clinic. MR volumetric Total intracranial volume (TIV), cerebellar volume (CV), right cerebellar volume (Rc), left cerebellar volume and mid-sagittal vermian area (M-SVA) was performed in both control and patient group. Microsoft excels statistic software wave use to analyze the data.

Result:

TIV volume shows no difference between control and patient groups (control group TIV=1477.6 vs patient group=1434.05ml). The TIV and cerebellum differed by sex, with mean male TIV=1545.9, female=1401.7, $p=0.0026<0.01$, mean male CV=149.9, female CV=133.8, $p=0.003<0.01$. After the CV/TIV normalization, there shows no difference of cerebellum between male and female

There is difference of C/TIV between control and patient group with mean control/patient C/TIV=0.0964/0.0881, $F=5.28$, $p=0.00074<0.01$, t-test $p=0.028<0.05$. No difference can be found in Mid-sagittal vermian area. We further evaluate and analyze the C/TIV among the different parameters. Only the symptomatic group shows significant decreased cerebellum volume as compared with the idiopathic group.

Conclusion:

Functional abnormality of cerebellum of variable cause might lower the threshold of seizure attack. We might predict the seizure tendency and do some prevention if we found cerebellar atrophy, basal ganglion atrophy in case such as post-head injury, post- cerebral hemorrhage and other organic brain lesion.

Key words: cerebellar volume, MRI volumetry, epilepsy,

Introduction:

It is estimated that about 0.23-1.9% of population have the problem of chronic epilepsy.[3] Anticonvulsants is the main treatment choice that followed by epileptic surgery (mainly Anterior temporal lobectomy), vagus nerve stimulation, deep brain and cerebellar stimulation and ketogenic diet control. About 72% of patient in clinical practice the etiology is unknown and classified as idiopathic or cryptogenic after general epileptic survey[3]. Under the much progress in genetic technique and MRI study, many previous so-called idiopathic, cryptogenic epilepsy was proved to be disorder of genetic origin such as channelopathy and cortical development abnormality (heterotopia, cortical microdysgenesis..). More understanding the pathophysiology of epileptogenic process there would be more efficacies in the management of epilepsy.

MRI volumetry is a reliable and reproducible method to evaluate structure lesion and disease process[4]. The most well known quantitative MRI volumetry is analyzing the volume of neocortex, cerebral volume, Hippocampus, amygdaloid and other temporal structure in patients with epilepsy and dementia, Schizophrenia. Rare report is about the volumetry of subcortical structure especially cerebellar volume in patients with epilepsy. Nuclear image study and animal study suggest that subcortical structure appear to serve as the anatomic structure that modulate propagation after the principle epileptogenic focus has emerged. Substantia nigra and cerebellum is part of a seizure-suppressing circuit[5].

Cerebellar atrophy and loss of Purkinje cells had been reported for more than 70 years in patients with chronic epilepsy. There were reports of MRI study show about 30% cerebellar atrophy in patients with chronic focal epilepsy.[7].Cerebellar atrophy has usually been considered as a consequence of recurrent seizures, phenytoin (PHT) intoxication[2], or other epilepsy related factors. Animal experiments and human study suggest inhibitory effects of the cerebellum on seizure activity. A structurally damaged cerebellum might be impaired in its inhibitory function and more prone to epilepsy. The same proposal as the subcortical structure atrophy such as thalamus and striatum might be a risk factor of epileptic disorder.[5] To investigate these hypothesis, we used MRI volumetric study to analyze cerebellar volume in chronic epileptic patients for further understand it' s role in the pathogenesis of epilepsy.

The aims of this study are to investigate 1.The difference of cerebellar volume

between normal subject and epileptic patient. 2.To analyze the relationships of volume atrophy related to the parameters such as seizure pattern, epileptic duration, onset age, drug duration, epileptic syndrome, and epileptic focus.

Methods:

A retrospective, cross-sectional, open labeled case controlled study.

Subject:

We have enrolled consecutive 15 epileptic patients 6 males and 9 female from our epileptic clinic, one with R parietal AVM, one with frontal meningioma, one with cerebral hemorrhage history, one with venous thrombosis, one with cortical dysgenesis, 3 with mesial temporal sclerosis, 7 with idiopathic. We exclude patients with acute provoking seizure such as acute CNS infection, post-traumatic and other chronic organic brain damage associated posterior fossa lesion induced seizure.

The basic data in each patient we record and analyze are epileptic duration (divided to 2 group, one group with duration less and equal to 5 years, the other over 5 years), drug duration (less and equal to 4 years vs. over 4 years), onset age of epilepsy (less than 20 years means early onset vs. late onset), focal or generalized predominant epilepsy, epileptic syndrome (idiopathic vs. symptomatic) epilepsy and epileptic focus TLE (temporal lobe epilepsy) vs. ETLE (extra temporal epilepsy) proved by clinical semiology and EEG evidence of epileptiform discharge.

Another 19 healthy age matched (subjects we have recruited from the database of neurological healthy examination department in our Hospital (CCH) for normal control. In both patient and control group we selected age less than 65 adult subjects.

MR Acquisition

All subject were scanned on 1.5 T high resolution Siemens Symphony MR scanner. Sagittal T-1 weight image (TE=15 TR=525) and a axial T2 weighted image (TE=96 TR=4000) were performed with matrix 256 x256; field of view [FOV], 22 x22cm, yielding contiguous, 19 contiguous 5-mm-thick slices and 1.5-2 mm gap on T1 series, 19 contiguous 2.0-2.5 mm gap on T2 series.

Image analysis

For reason of inter-individual variation of head size and sex, we use Total intracranial volume (T2 axial section TIV) to normalize the cerebellar structure volume[6]. The contents of TIV included parenchyma, CSF and meninges. The measurement of TIV is every slice between the inferior limit of segmentation, set at foramen magnum, and the superior point of the cortex was measured. Cerebellar volume measurement is every slice between the most upper and lower cerebellar segmentation. We also

measure the R cerebellar, L cerebellar volume and mid-sagittal vermian area from T-1 weight sagittal view. The MRI data set was transferred to a MRI workstation. We do the work of volumetry by mouse manual drawing of structure contours (Fig A, B, C) with the aid of automatic area calculation. The TIV and cerebellar volume was calculated by multiplying summation area of each slice with slice thickness plus gap. Brain segmentations were performed on all controls and epileptic patients and manually checked and edited to ensure accuracy.

Statistic methods

Data was analyzed with Microsoft excel. Un-paired t-test was used to compare the age and TIV between control and patient groups for match control, paired t-test to compare the volume between Right and L cerebellum volume. Cerebellum/TIV ratio was used to normalize the variation of head size and sex factor.

We use F distribution test to analyze the difference of corrected cerebellum between patient and control group and use un-paired t test to analyze the cerebellum volume between patient groups related to each parameter.

RESULT:

As the Table 1 and 3 show, The T2 weighted mean TIV volume shows no difference between control and patient groups (control group TIV=1477.6 vs patient group=1434.05ml). The TIV and cerebellum differed by sex, with mean male TIV=1545.9, female=1401.7, $p=0.0026<0.01$, mean male CV=149.9, female CV=133.8, $p=0.003<0.01$. After the CV/TIV normalization, there shows no difference of cerebellum between male and female (FIG E). By the way, right cerebellar volume is larger than the Left cerebellar volume in the T1 weighted sagittal evaluation (FIG F:). Cerebellum volume shows minor decrease as considering the age with Pearson's correlation coefficient= -0.272 (FIG D:).

As the document of table 2: and FIG G: that there is difference of C/TIV between control and patient group with mean control/patient C/TIV=0.0964/0.0881, F=5.28, $p=0.00074<0.01$, t-test $p=0.028<0.05$. No difference can be found in Mid-sagittal vermian area. For the sake of variance difference between patient and control group, we further evaluate and analyze the C/TIV among the different parameters (early onset vs late onset, epileptic duration, drug treatment duration, partial vs generalized seizure, idiopathic vs symptomatic epilepsy, TLE vs ETLE). Only the symptomatic group shows significant decreased cerebellum volume as compared with the idiopathic group (FIG I:).

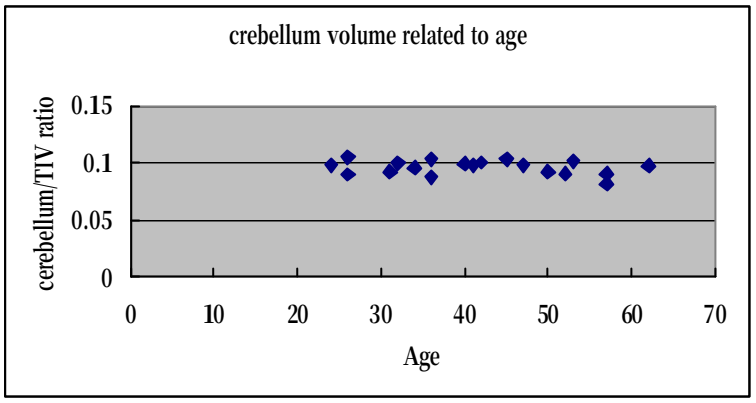
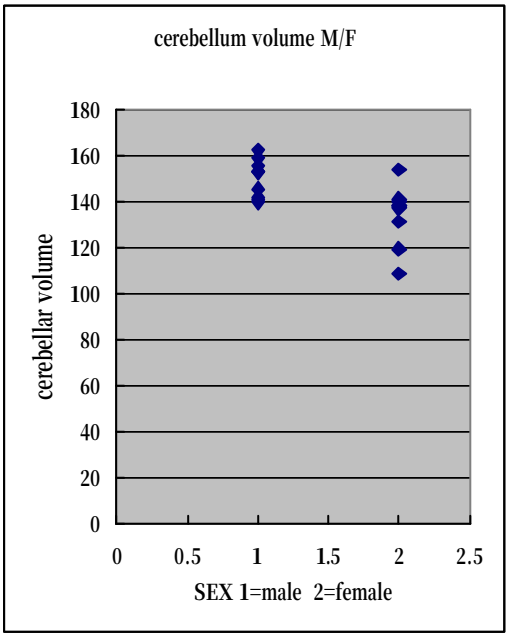


FIG D: age effect in control group, Correlation coefficient= - 0.272



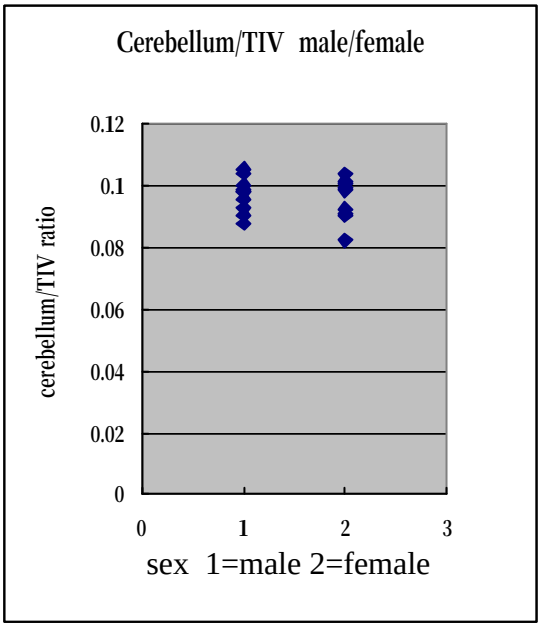


FIG E: mean cerebellum volume male=149.974, female=133.879 ml, p=0.0035< 0.005,

Cerebellum/TIV correction Male= 0.097, Female=0.095 P=0.587>0.05

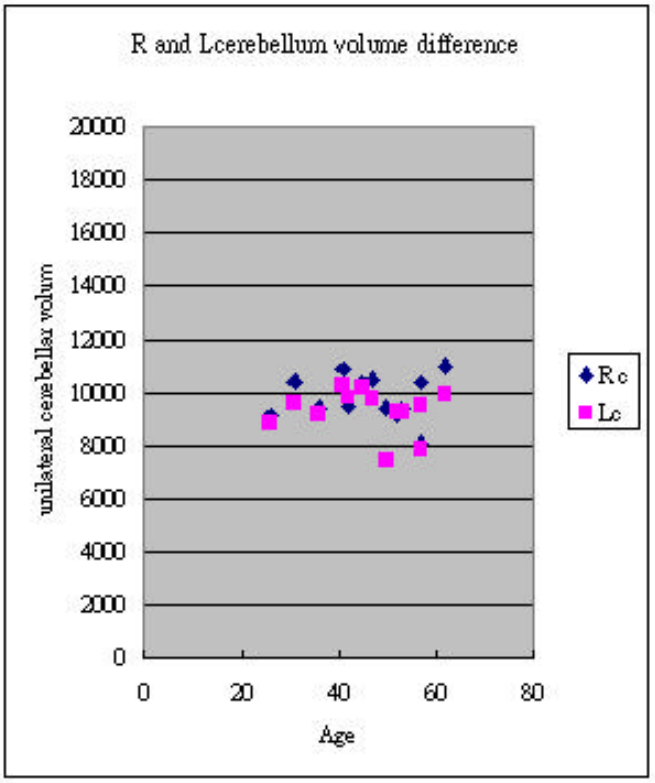


FIG F: Rc=Right cerebellum Lc=Left cerebellum

Mean Rc=63.79 Lc=60.39, Pearson' s correlation= 0.74

P= 0.0045<0.05

Table 1 Cerebellar volumes of 19 healthy age-matched control

Male control	Age/years	TIV	CV	C/TIV	M-SVA	RC	LC
1	45	1523.663	158.39	0.104	898	67.295	66.098
2	41	1571.918	154.97	0.0986	1051	70.759	66.514
3	47	1476.144	145.26	0.0984	1018	68.198	63.622
4	31	1526.961	141.55	0.0927	1018	67.652	62.491
5	62	1421.661	139.33	0.098	1310	71.338	64.324
6	36	1745.253	153.08	0.0877	969	61.269	59.637
7	57	1546.955	140.25	0.0907	823	67.483	61.821
8	26	1534.176	161.73	0.1054			
9	32	1519.279	152.49	0.1004			
10	34	1593.246	152.68	0.0958			
Female control							
1	42	1391.925	139.99	0.1006	1065	61.497	63.667
2	53	1287.468	130.89	0.1017	984	60.879	60.118
3	52	1520.258	137.96	0.0907	1128	59.677	60.183
4	57	1316.606	108.4	0.0823	1026	52.54	50.914
5	26	1510.902	136.65	0.0904	1114	59.391	57.681
6	50	1288.369	119.12	0.0925	1161	61.295	48.113
7	24	1556.968	153.56	0.0986			
8	36	1325.366	137.54	0.1038			
9	40	1417.845	140.81	0.0993			

Table 1:TIV=total intracranial volume (cm^3), CV=cerebellar volume (cm^3), C/TIV= cerebellum/TIV ratio, M-SVA=mid-sagittal vermian area (cm^2), RC=R cerebellar volume (cm^3), LC=L cerebellar volume (cm^3)
Male mean TIV=1545.9, female=1401.7, $p=0.0026<0.01$,

Basic data of patient group

Patients	Age on exam	Sex	CV	C/TIV	M-SVA	onset age	duration of epilepsy	duration of drug	seizure type partial/GTC	epileptic location	Etiology
1	24	M	131.424	0.0846	872	19	6	3	CPS GTC	TLE	IDIOPAHIC
2	28	M	133.65	0.0975	976	20	8	8	GTC CPS	TLE	IDIOPAHIC
3	59	M	103.517	0.0655	882	60	0	0	Partial	ETLE	ICH
4	37	M	146.0094	0.0885	1288	30	6	0	GTC partial	ETLE	R AVM
5	55	M	110.273	0.0759	979	55	0	0	GTC partial	ETLE	frontal meningioma
6	61	M	162.505	0.1074		61	0	0	GTC partial	ETLE	IDIOPAHIC
7	23	F	128.156	0.1009	952	5	19	19	GTC Partial	ETLE	IDIOPATHIC
8	27	F	131.3475	0.108	1085	12	16	16	GTC CPS	ETLE	IDIOPATHIC
9	34	F	117.922	0.0811	1004	32	2	2	GTC Partial	ETLE	venous thrombosis
10	17	F	127.876	0.0894	959	13	4	2	GTC	TLE	L MTS
11	41	F	74.433	0.0584	841	8	32	32	GTC CPS	ETLE	R p-o degeneration, R MTS
12	25	F	129.556	0.0886		22	5	4	GTC CPS	TLE	R MTS
13	23	F	122.744	0.0907		19	6	4	GTC CPS	TLE	L MTS
14	19	F	132.664	0.0937		17	4	3	GTC	ETLE	IDIOPATHIC
15	47	F	120.525	0.079		45	2	1	GTC	TLE	IDIOPATHIC

Table 2: CV=cerebellar volume, C/TIV= cerebellum/TIV ratio,

M-SVA=mid-sagittal vermian area, TLE=temporal lobe epilepsy, ETLE= extratemporal epilepsy

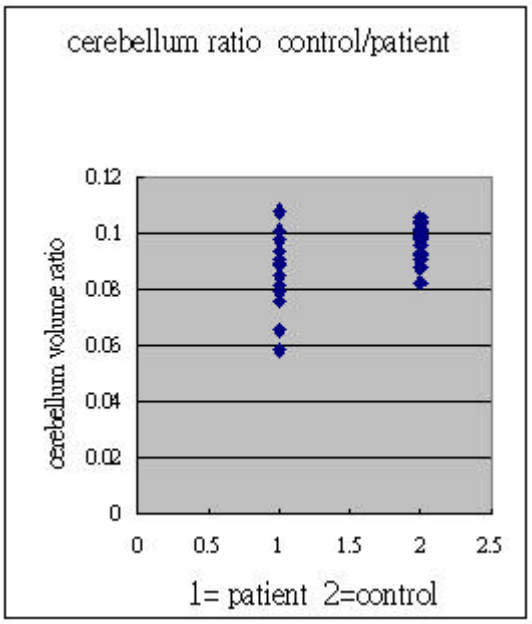


FIG G: cerebellum/TIV ratio comparison between patient and control group F=5.28, p=0.00074<0.01

T-test p=0.028<0.05

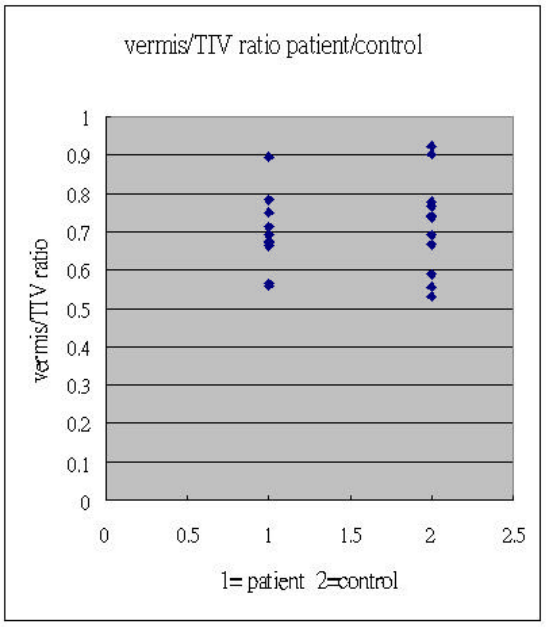


FIG H: vermis/TIV ratio comparison between patient and control group t-test p=0.64>0.05

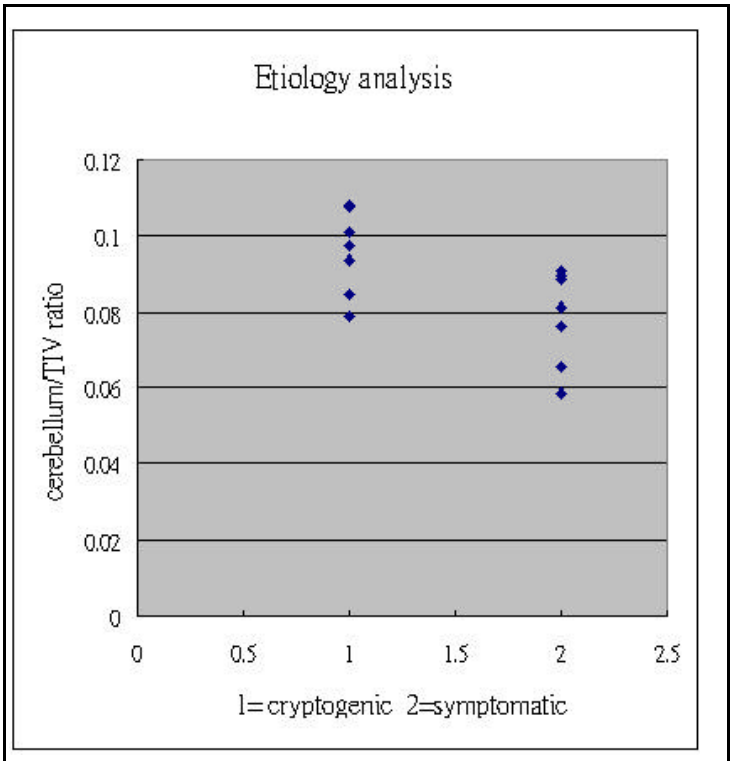


FIG I: idiopathic vs symptomatic t-test p=0.0092<0.01

Table 3 Comparison of volumetric/planimetric data for all control and patient group

	Control group	*patients group*		
Gender (no M/F)	10/9	6/9		
Age(mean, range; years)	41.63 (24, 62)	35 (17, 61)	p=0.13 >0.05	p=0.13 >0.05 t=2.03 (2 tail)
TIV cm^3 (mean, st.dev; cm^3)	1477.6296 118.45	1434.0568 122.18055	p=0.301>0.05	p=0.301>0.05 t=2.04 (2 tail)
cerebellar volume (mean, st.dev; cm^3)	142.35005 13.273572	124.84013 19.662113	F=0.456 t=2.063	**p=0.059>0.05** **p=0.0068<0.01**
C/TIV ratio (mean, st.dev; cm^3)	0.0963988 0.0062	0.0881364 0.013	F=5.28 p=0.028 t test	**p=0.00074<0.01**
M-SVA (mean, st.dev; cm^2)	1043.462 121.7734	983.8 128.3016	F=0.9 t=2.093	p=0.423>0.05 p=0.272>0.05

Table 3: comparison data between patients and control groups

Discussion:

In this study, we know there were differences of TIV between sex and without difference related to age. The difference of cerebellar volume can be normalized by TIV correction.[8] It prove that our methods is reproducible and reliable. The asymmetry related to right and left cerebellum could be due to the handed type but we fail to detail the personal history. Originally the purpose we check the unilateral cerebellar volume was to solve the question that if the epileptic focus were related to the change of different unilateral cerebellar volume, however the case number was not adequate to analyze.

The etiology of cerebellar atrophy and degeneration in epileptic patients is still of no definite answer. Frequent repeated seizures induced hypoxia and brain edema, anticonvulsants toxicity and the hypothesis that cerebellar atrophy exist before and related to the etiology of epilepsy[2] all were considered to be probable factors.

There were several case reports with the pathologic data show that cerebellar atrophy was due to the sequel of acute phenytoin intoxication as well as chronic drug treatment with related to drug dosage and duration[1]. In our case series all the patients took the same dosage of phenytoin 300mg per day without definite phenytoin intoxication history and with variable other anticonvulsants and the drug treatment duration shows questionable influence on the cerebellar volume.

The analysis in our case series revealed that cerebellar atrophy is apparent with statistic significance in the symptomatic epileptic patient as compared with idiopathic patients and there were no apparent cerebellar volume difference as considering the factor such as epileptic duration (acute vs chronic case), onset age and epileptic focus. Recent preliminary cohort prospective MRI volumetric study[8] shows the cerebellar atrophy is more apparent in chronic epileptic patient and not present in newly diagnosed epileptic patients. However the enrolled case series in that study is different from our case series in that they excluded the cases with organic brain lesion found in the MRI study. In our case series there were newly onset cases with organic lesion such as frontal meningioma and parietal AVM. The case series in that study might be the idiopathic epileptic disorder. We propose that in idiopathic epileptic patient the main causes of cerebellar atrophy might be due to the impact of epileptic duration and drug toxicity. In symptomatic epileptic patients, the cause of cerebellar atrophy were

variable and small cerebellar volume is a predisposing factor to seizure attacks that is why not every brain tumor, every cerebral hemorrhage…and every other organic brain lesion cases suffer seizure disorders. Seizure itself and drug toxicity induced cerebellar atrophy in symptomatic epilepsy may need more large case number and longitudinal study to investigate.

In our patient series mid-sagittal vermian area (M-SVA) was not smaller as compared with control subjects yielding different result as considering total cerebellar volume. It might mean that the epileptic inhibitory function of cerebellum were in the cerebellar hemisphere not vermis. The result is different as compared with previous MRI study that shows vermian atrophy in chronic epileptic patient[8].

Conclusion:

Cerebellum is well known motor planning center and basal ganglion motor modulating center. Functional abnormality of cerebellum of variable cause might lower the threshold of seizure attack if there were a cortical epileptogenic lesion as of basal ganglion[5].

We might predict the seizure tendency and do some prevention if we found cerebellar atrophy, basal ganglion atrophy in case such as post-head injury, post-cerebral hemorrhage and other organic brain lesion.

The cause of cerebellar atrophy might be due to multifactor. The influence of drug intoxication and damage of seizure itself might be in minor degree not as prominent as symptomatic factors does, it needs more strict case control, longitudinal study to investigate.