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Magnetic resonance imaging (MRI) based cerebellum and brain volume measurement using cavalier principle in epilepsy patients on long-term phenytoin and carbamazepine therapy

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ABSTRACT

Aims: This study aims to evaluate cerebellar atrophy findings in epilepsy patients using long-term antiepileptic drugs by calculating cerebellum/brain volume ratios with the Cavalieri principle and comparing this method with other volumetric measurement techniques.

Methods: A total of 30 patients diagnosed with epilepsy and receiving long-term phenytoin or carbamazepine treatment between January 2004 and May 2005, along with a control group of 15 individuals, were included in the study. Magnetic resonance imaging (MRI) was performed using a 0.2 Tesla open MRI system. Brain volumes and cerebellum/brain volume ratios were calculated using the point-counting method based on the Cavalieri principle.

Results: No statistically significant difference was found between the calculated volume values of the phenytoin, carbamazepine, and control groups ($p>0.05$). However, in one patient using phenytoin, the cerebellum volume was found to be significantly low, consistent with cerebellar atrophy.

Conclusion: Larger studies are needed to determine whether long-term use of phenytoin and carbamazepine leads to cerebellar atrophy. The point-counting method based on the Cavalieri principle may offer a practical and applicable alternative for routine clinical use.

Keywords: Cerebellar atrophy, epilepsy, phenytoin, stereology, Cavalieri principle

INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders affecting millions of people worldwide. Antiepileptic drugs (AEDs) form the cornerstone of epilepsy treatment; however, their long-term use has been associated with certain neurotoxic effects. Some studies suggest that AEDs, such as phenytoin and carbamazepine, may contribute to cerebellar atrophy (shrinkage of the cerebellum), leading to motor coordination deficits and balance issues. However, it remains unclear whether cerebellar atrophy is solely related to drug use or whether the frequency and duration of seizures also play a role.

The primary aim of this study is to assess the presence and degree of cerebellar atrophy in epilepsy patients on long-term phenytoin and carbamazepine therapy. To achieve this, cerebellar volume and cerebellum-brain ratios were calculated using magnetic resonance imaging (MRI) combined with the Cavalier principle-based point-counting technique and compared to a control group. This study aims to objectively assess the effects of epilepsy medications on cerebellar volume and contribute to more reliable diagnostic methods in clinical practice. Furthermore, the findings may highlight the importance of personalized approaches in epilepsy treatment.

METHODS

Ethics

This article is derived from the medical specialty thesis of Dr. Mustafa Yalçın, conducted at Isparta Süleyman Demirel

University in 2005. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study examines epilepsy patients who have been on phenytoin or carbamazepine therapy for at least five years. Individuals without other neurological disorders, metabolic conditions, or structural brain pathologies, and who had complete MRI scans, were included. A total of 45 individuals participated: 15 on phenytoin therapy, 15 on carbamazepine therapy, and 15 healthy controls. Participants were matched for age, gender, and body-mass index (BMI).

Imaging Protocol

All patients and the control group underwent sagittal T1-weighted MRI scans using a 0.2 Tesla open MRI system. A standard neuroimaging protocol was followed during the MRI scans. Head supports were used to standardize head positioning, and participants were instructed to remain still during the scan. Individuals with motion artifacts in their scans were excluded from the study. Additionally, all participants underwent a neurological examination prior to imaging and were assessed for signs of cerebellar dysfunction.

Volume Calculation and Applied Formulas

Cerebellum and brain volumes were calculated using the Cavalier principle-based point-counting method. The brain and cerebellum areas were analyzed across predefined slice intervals to obtain the total volumes. The point-counting method relies on counting the number of grid points that intersect the target region in each slice. The point-counting method based on the Cavalieri principle was applied (**Figure 1**).

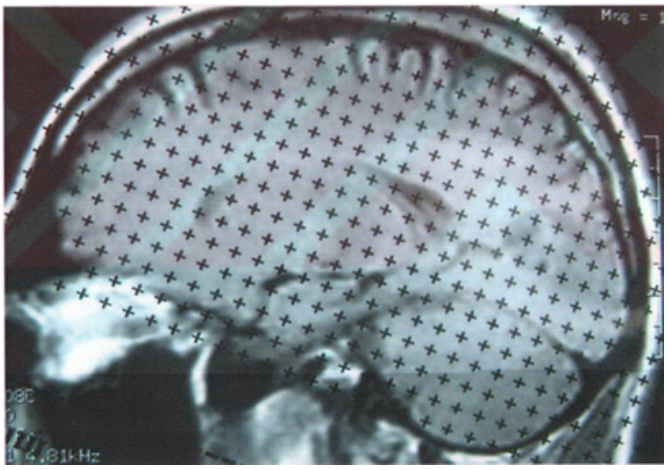

Figure 1. Random point grid superimposed on cross-sections for area estimation

The formula used for volume calculation is as follows: $V=t\times\sum P\times a(p)$

Where:

•V=Volume (mm^3)

•t=Slice thickness and slice interval (mm)

•P=Number of points in each slice

•a(p)=Area represented by each point (mm^2)

This formula allows the volume estimate to account for the gap between slices and the total area calculated in each slice. The point-counting process involves determining the number of grid points in each slice that cover the cerebellum.

The cerebellum-brain volume ratio was calculated as: Ratio=V_cerebellum/V_brain×100

This ratio was used as a comparative metric in cerebellar atrophy assessment and helped identify differences among patients.

Measurements were performed by two independent observers, and intra-observer and inter-observer reliability were assessed. Bland-Altman analysis was applied to determine statistical consistency.

Statistical Analysis

The data analyses were performed using SPSS 22.0 software. Volume differences between groups were analyzed using the Kruskal-Wallis test. Pairwise comparisons were made using the Mann-Whitney U test. The correlation between cerebellar volume and cerebellum-brain ratios was evaluated using Spearman correlation analysis. A p-value of <0.05 was considered statistically significant. Additionally, multivariate logistic regression analysis was conducted to control for the effects of age and gender.

RESULTS

Cerebral and cerebellar volumes, as well as cerebellum-to-brain volume ratios, were calculated in patients receiving phenytoin or carbamazepine and in healthy controls using the point-counting method based on the Cavalieri principle. The mean cerebellar and total brain volumes, along with cerebellum-to-brain ratios and standard deviations, are presented below. The calculated cerebellar and total brain volumes of patients receiving phenytoin are presented in **Table 1**.

Table 1. Calculated cerebellar and total brain volumes and cerebellum/brain ratios for phenytoin users

Patient	Cerebellum volume (mm^3)	Total brain volume (mm^3)	Cerebellum/ brain ratio, (%)
1	165	1684	9.79
2	147	1287	11.43
3	133	1100	12.11
4	130	1308	9.96
5	123	1313	9.34
6	150	1349	11.16
7	137	1406	9.76
8	120	1195	10.05
9	125	1283	9.74
10	119	1135	10.51
11	96	1048	9.19
12	123	909	13.52
13	130	1135	11.46
14	155	1202	12.86
15	124	1082	11.46

Comparative analysis revealed no statistically significant differences in volume parameters among the phenytoin, carbamazepine, and control groups ($p>0.05$). However, one

individual in the phenytoin group demonstrated a markedly reduced cerebellum-to-brain ratio (7.7%), the lowest observed across all cohorts and consistent with radiological evidence of atrophy. Visual inspection of MR images demonstrated widened cerebrospinal fluid spaces consistent with cerebellar atrophy. Corresponding values for carbamazepine users are shown in **Table 2**.

Table 2. Cerebellar and brain volumes and their ratios for carbamazepine users

Patient	Cerebellum volume (mm^3)	Total brain volume (mm^3)	Cerebellum/ brain ratio (%)
1	132	1119	11.80
2	119	1156	10.32
3	118	1134	10.44
4	140	1153	12.14
5	138	1390	9.94
6	134	1218	10.99
7	127	1097	11.55
8	123	1230	9.98
9	131	1221	10.71
10	123	1101	11.00
11	121	1165	10.41
12	105	1254	8.37
13	94	853	11 03
14	101	1028	9.81
15	107	1050	10.17

No statistically significant differences were found between the carbamazepine group and either the phenytoin or control groups (p>0.05). Group comparisons of cerebellar volume, brain volume, and cerebellum-to-brain ratio are summarized in **Figure 2**.

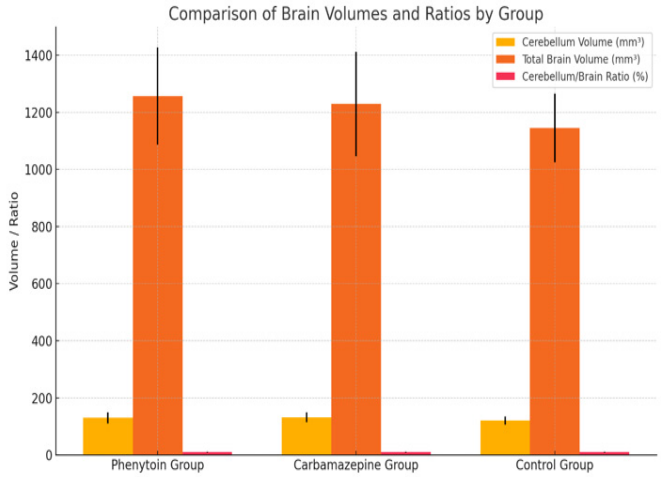

Figure 2. Mean cerebellar and brain volumes, and cerebellum/brain volume ratios with standard deviations across groups

Comparison of cerebellar volume, total brain volume, and cerebellum-to-brain ratio among the study groups. The chart displays mean values±standard deviations for each parameter across the phenytoin group, carbamazepine group, and healthy controls. While total and regional brain volumes differ among groups, the cerebellum-to-brain volume ratio remains relatively stable, indicating proportional preservation despite overall volumetric variations.

There were no statistically significant differences among groups in cerebellum-to-brain volume ratios (p>0.05).

Cerebellar atrophy is a frequent finding in chronic epilepsy patients and has been associated with long-term phenytoin usage. Multiple pathophysiological mechanisms have been proposed, including direct toxicity to Purkinje cells, degeneration of cerebellar afferent pathways, and seizures themselves leading to hypoxia-induced injury. Some studies suggest a synergistic role of genetics in increasing susceptibility to these effects.[1-3]

Imaging modalities such as CT, MRI, MR volumetry, MR spectroscopy, and diffusion tensor imaging have all been used to assess cerebellar atrophy.[4-7] Notably, cerebellar atrophy is considered a marker of poor prognosis in epilepsy and may influence surgical decision-making, including temporal lobectomy.[8,9]

In our study, no significant differences were observed between the phenytoin, carbamazepine, and control groups. However, one subject on phenytoin therapy exhibited both a reduced cerebellum/brain volume ratio and radiological signs of cerebellar atrophy, in the absence of confounding variables. This supports the potential of phenytoin to induce isolated cases of cerebellar atrophy, in line with previous literature.[10-13]

Multivariate logistic regression analysis, adjusted for age and gender, showed no significant association between antiepileptic drug type (phenytoin vs. carbamazepine) and cerebellum-to-brain volume ratio (p>0.05). Similarly, neither age nor gender independently predicted cerebellar volume reduction in this cohort.

Carbamazepine showed no such effect, aligning with prior findings that it does not independently cause cerebellar atrophy, although caution is advised in patients with pre-existing cerebellar degeneration.[8-14]

Our results reinforce the utility of the Cavalieri principle in delivering reliable volumetric assessments, with coefficients of error remaining below 5% in all cases. The technique offers a cost-effective, efficient alternative for tracking volumetric changes in neurological patients.

An important limitation of the present study is the relatively small sample size (n=45). This limited number of participants reduces the statistical power of the analyses and may have obscured subtle volumetric differences among the groups. Therefore, the absence of significant findings should be interpreted with caution. Larger, prospective, multicenter studies are warranted to provide more definitive conclusions.

DISCUSSION

This study aimed to evaluate the effects of commonly used AEDs, phenytoin and carbamazepine, on cerebellar volume. The results revealed no statistically significant difference between groups. However, cerebellar atrophy was detected in a phenytoin user, indicating potential long-term neurotoxic effects of phenytoin. The outlier case with a markedly low

cerebellum-to-brain ratio (**Table 1**) supports the potential for phenytoin-related neurotoxicity.

Previous studies have shown that phenytoin use may contribute to dose-dependent cerebellar atrophy. Long-term phenytoin use can lead to Purkinje cell loss, significantly reducing cerebellar volume. Animal studies suggest that phenytoin may trigger neuronal degeneration by increasing oxidative stress levels. Human studies have reported that neurodegenerative effects are dose-dependent.

Cerebellar atrophy in epilepsy patients may not solely be due to medication use; the frequency and duration of seizures could also play a significant role. Chronic seizure activity may lead to neuronal loss in cerebellar structures through hypoxia and inflammation. Some studies suggest that although cerebellar volume reduction is observed in epilepsy patients, these changes may be more strongly associated with drug effects rather than seizure frequency.

In this study, the Cavalier principle-based point-counting technique was used for cerebellar volume assessment. This technique provides more precise volume measurements compared to manual or visual evaluations. Both phenytoin and carbamazepine users were analyzed separately and compared with the control group, enabling a more comprehensive evaluation of the effects of different drugs on cerebellar structures. The analysis of patients who have been on AEDs for at least five years is crucial for determining the long-term neurological effects of these medications.

When comparing our findings to the existing literature, some inconsistencies were noted. For instance, earlier research has demonstrated cerebellar volume loss associated with long-term phenytoin use, although our findings did not show a statistically significant difference among groups. This discrepancy may be due to sample size, MRI resolution, and individual patient variability. Other studies have also examined the effects of multiple AEDs on cerebellar volume, with carbamazepine being suggested to have less neurotoxic effect.

Recent evidence has reinforced the association between long-term antiepileptic drug exposure and cerebellar structural alterations. Prolonged use of phenytoin has been linked to irreversible cerebellar damage, particularly due to Purkinje cell vulnerability.[15] Mechanistic pathways underlying chronic drug exposure and cerebellar degeneration have also been described.[16] From a methodological standpoint, normative modeling approaches have been introduced to improve volumetric MRI biomarkers, thereby enhancing sensitivity in heterogeneous epilepsy cohorts.[17] Furthermore, structural and functional cerebellar abnormalities have been demonstrated in temporal lobe epilepsy using volumetric, diffusion, and connectivity-based analyses.[18] A systematic review additionally emphasized that phenytoin exposure, poor seizure control, and long disease duration remain consistent risk factors for cerebellar degeneration.[19] Taken together, these contemporary findings suggest that our results should be interpreted within the context of technological advances and larger datasets that have emerged since the time of data collection. Although the use of a low-field MRI scanner and limited sample size may have prevented the detection of subtle changes, the Cavalieri principle remains a valuable volumetric method that can complement modern imaging approaches.

The use of a low-field MRI scanner in our study may have limited the detection of subtle morphological changes. Future studies using high-field MRI systems could provide clearer insights into the relationship between cerebellar atrophy and AED use. Moreover, long-term prospective studies are needed to assess the progressive nature of cerebellar atrophy over time.

Another limitation of this study is the sample size. Larger, multicenter studies would improve the generalizability of the findings. Furthermore, future research should consider the detailed neurological histories of patients, including seizure type and duration, to evaluate their effects on cerebellar atrophy more comprehensively. Genetic factors may also contribute to cerebellar atrophy in epilepsy patients, and pharmacogenetic studies could help identify individuals more susceptible to phenytoin's neurotoxic effects.

Limitations

A major limitation of our study is that the data were collected nearly two decades ago using low-field MRI technology. Since then, substantial progress has been made in neuroimaging, including automated volumetric methods, radiomics, and ultra–high-field (7T) MRI, which enable more sensitive and reliable assessment of subtle volumetric changes. Nevertheless, by applying the Cavalieri principle to this historical dataset, our study provides methodological insights that remain relevant, especially for centers where advanced imaging resources are limited. When considered in the context of more recent investigations,[15,16,18] our findings underscore the need for large-scale, prospective studies to confirm the long-term neurotoxic effects of phenytoin and to further elucidate the role of the cerebellum in epilepsy.

Although there is strong evidence supporting phenytoin's neurotoxic effects, the absence of cerebellar atrophy in some patients suggests that individual genetic and metabolic differences may play a role. Future research focusing on pharmacogenetics could help identify patients at higher risk for neurological side effects and enhance personalized epilepsy treatment. As this study is retrospective, long-term prospective follow-up studies are needed to evaluate the The retrospective nature of our study constitutes another limitation, as it prevents us from establishing causal relationships and from monitoring progressive changes over time. Prospective, longitudinal follow-up studies would be more suitable for clarifying the temporal relationship between long-term antiepileptic drug exposure and cerebellar atrophy. Progressive nature of cerebellar atrophy over time.

CONCLUSION

The Cavalier principle-based point-counting technique is an objective and feasible method for assessing cerebellar atrophy in epilepsy patients. However, further large-scale, long-term studies using high-field MRI scanners are necessary to clarify the relationship between AED use and cerebellar atrophy.

Future research should also examine the effects of seizure duration and frequency on cerebellar atrophy. Personalized drug selection and seizure management are critical strategies for minimizing cerebellar degeneration in epilepsy patients.

Finally, it should be acknowledged that this study was conducted nearly 20 years ago using a low-field MRI scanner, which limits its applicability to current clinical practice. Advances in high-field MRI, automated volumetry, and radiomics now provide superior methods for assessing cerebellar atrophy. Nonetheless, our findings demonstrate the feasibility and reproducibility of the Cavalieri principle and emphasize the importance of historical data in shaping contemporary research directions.

This study demonstrated that long-term use of phenytoin and carbamazepine did not result in statistically significant differences in cerebellar or total brain volumes when compared to healthy controls. However, an isolated case of cerebellar atrophy was observed in a patient receiving phenytoin, suggesting that individual susceptibility or drug-specific neurotoxic effects may still play a role. The Cavalieri principle-based point-counting method proved to be a reliable and practical approach for volumetric assessment, with low measurement error and consistent reproducibility. While our findings do not support a generalized association between long-term carbamazepine or phenytoin use and cerebellar volume reduction, they highlight the importance of monitoring individual patients for potential neuroanatomical changes. Larger, prospective, and high-resolution imaging studies are warranted to clarify the long-term neurological effects of AEDs and to further evaluate the contribution of seizure frequency, genetic predisposition, and treatment duration. Personalized treatment strategies remain essential in minimizing neurological side effects and optimizing outcomes in patients with chronic epilepsy.

Another limitation of our study is the use of a low-field (0.2 Tesla) MRI scanner, which inherently restricts spatial resolution and sensitivity to subtle volumetric alterations. This technical limitation may have reduced the ability to detect mild degrees of cerebellar or cerebral volume loss. Future investigations should utilize high-field MRI systems (≥1.5 Tesla or 3 Tesla), which provide superior image quality and volumetric precision.

ETHICAL DECLARATIONS

Ethics Committee Approval

This article is derived from the medical specialty thesis of Dr. Mustafa Yalçın, conducted at Isparta Süleyman Demirel University in 2005.

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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