

Original Research Article

The effects on carotid artery intima-media wall thickness and development of atherosclerosis in children on anti-epileptic drug monotherapy

Rosina Ksoo^{1*}, Rakesh Sharma¹, R. K. Kaushal¹, Anupam Jhobta²

¹Department of Paediatrics, ²Department of Radiodiagnosis, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

Received: 28 March 2017

Accepted: 27 April 2017

*Correspondence:

Dr. Rosina Ksoo,
E-mail: rksoo.91@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Children with seizure disorder and requiring long-term anti-epileptic drugs are predisposed for development of atherosclerosis. We monitored the carotid artery intima wall thickness of the children on Anti-epileptic drug monotherapy along with their lipid profile for a period of one year.

Methods: Children under 18 years, who were newly diagnosed with epilepsy or were already on anti-epileptic drug monotherapy were included in the study period of one year. They were then prospectively followed-up at three months and again between the sixth and twelfth month's period. A high-resolution B-mode ultrasound using a 5-7 MHz linear transducer was employed for measuring the thickness of the carotid intima-media thickness (cIMT). The biochemical parameters including fasting lipid profile, body mass index and dietary habits were also taken.

Results: A total of 130 children were included in the study. The values of cIMT observed were 0.38 mm (0.1 mm) and 0.41 mm (0.1mm) in the new (control) and old cases respectively. The values of cIMT were significantly increased in patients receiving Carbamazepine (CBZ) and Phenytoin after 3 months of therapy and with increase in age and duration of intake of anti-epileptic drugs. There were no gender differences in the value of cIMT.

Conclusions: The values of serum cholesterol, LDL and HDL were significantly increased in children on CBZ and valproic acid. There was no difference in the lipid profiles of children on Phenytoin and Phenobarbitone. However, the atherogenic indices of the children taking any of the four anti-epileptic drugs were normal.

Keywords: Anti-epileptic drugs, Atherosclerosis, Carotid IMT, Monotherapy, Seizure

INTRODUCTION

Seizures are common in the pediatric age group and occur in ≈10% of children. About 70-80% of the patients who develop epilepsy may expect to have their seizures controlled with optimal antiepileptic therapy. The cumulative lifetime incidence of epilepsy is 3% and more than half of the cases begin in childhood. However, the annual prevalence of epilepsy is lower (0.5-0.8%) because many children outgrow epilepsy.¹

Epidemiological, clinical and experimental investigations have shown that anti-epileptic drugs (AED) predispose to atherosclerosis by altering the lipid profile.² It has been well documented that atherosclerotic vascular alterations may start early in life and progress with age.³ The first signs of hyperlipidemia can be detected in childhood and fatty streaks, which are the earliest pathologic lesions of atherogenic process, can be observed in the aorta and coronary arteries of individuals by the age of 20.^{4,5} Non-invasive measurement of carotid intima-media thickness

(cIMT) by high resolution B-mode ultrasound is widely used in observational studies and validated as a surrogate marker for early prediction of atherosclerosis.⁶ Phenytoin, Carbamazepine (CBZ), Valproic acid (VPA) and Lamotrigine are the commonly used AED for monotherapy.⁷ No such study has been carried out in this region, therefore, this study was planned to study the effects of AED on atherosclerotic changes by measuring the cIMT, lipid profiles and monitoring the atherogenic indices of the anti-epileptic drugs that were prescribed.

METHODS

The study was a hospital-based observational prospective study.

Inclusion criteria

All children with epilepsy below the age of 18 years, attending the OPD or were admitted in the Department of Pediatrics who were on AED monotherapy were included in the study for a period of one year from June 2011 till May 2012.

Exclusion criteria

Those with hepatic or renal diseases, with known family history of obesity, atherosclerosis or metabolic diseases and children who did not complete at least two follow-up visits were excluded.

In the first visit, a brief clinical history, age, sex, weight, dietary history, body mass index (BMI), fasting lipid profiles, AED use and duration of therapy was noted.

Measurement of cIMT

cIMT were measured by B-mode ultrasound using a 5-7 MHz linear transducer on Xario XG Toshiba Ultrasound machine. The patients were examined in supine position with the neck extended and the probe placed in the antero-lateral position. The intima-media thickness (IMT) is defined as the distance between the intima-blood interface and the adventitia-media junction (Figure 1). After freezing the image, the measurements were made using electronic calipers. The maximum thickness of the intima-media width was measured to give three readings and the mean value was used for statistical purposes. The cIMT values of the newly diagnosed cases of epilepsy, before initiating treatment was taken as the control values for the study. This measurement was again repeated on follow-up between 6 months and 12 months' period.

Biochemical testing for lipid-profiles

For testing of biochemical parameters, 2 ml of fasting venous blood from the patients was obtained and sent for liver function test and lipid profiles. Estimation of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) concentration were

determined by photometric methods using a commercially available kit (AGAPPE Diagnostics) in an Auto-analyzer (KONELAB 30).⁸⁻¹⁰ Low-density lipoprotein cholesterol (LDL-C) was directly calculated using the Friedewald formula (Friedewald et al, 1989): $LDL-C = TC - (HDL-C + 0.2TG)$.¹¹ Very-low density lipoprotein cholesterol (VLDL-C) was also directly calculated using the Friedewald (1989) formula: $VLDL-C = TG/5$.¹¹ The atherogenic indices were calculated from the three ratios of cholesterol and HDL; LDL and HDL and triglycerides and HDL. This test was repeated on follow-up at 3 months and again between 6th and 12th months period. The lipid profiles of the new cases measured at the time of diagnosis was taken as the control values for those children who were already on long-term AED.

The minimum time for the intake of antiepileptic medication included under old cases was taken as 3 months. The case details and data were entered in a pre-defined excel worksheets.

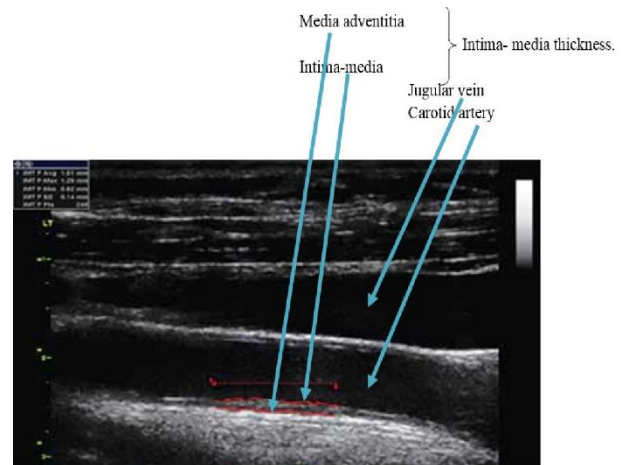


Figure 1: Showing measurement of carotid intima-media thickness (cIMT).

Statistical analysis

Data is analyzed using SPSS software 20. Values were expressed as mean (SD). When the number of independent groups was limited to two, the Student's t-test was used. The significance of the differences between more than two groups was evaluated applying the non-parametric one-way analysis of variance (ANOVA). Significance of differences in terms of medians was evaluated between the groups. In instances of significant results with the Kruskal-Wallis test (ANOVA), non-parametric multiple comparison tests were used to identify the conditions that caused the difference.

Finally, multiple stepwise linear regression analysis was used to examine relationships between mean IMT and all other variables investigated. F value is the measurement of distance between individual distributions. As F value

goes up, P goes down (i.e., more confidence in there being a difference between two means).

RESULTS

A total of 165 children were enrolled during the study period but only 130 children were included for analysis. The others were dropped out due to incomplete testing for all parameters (n=7) or were lost to follow-up (n=25) and for some cases, a second drug was added for the control of epilepsy (n=3). Of the 130 cases, 74 were males and 56 were females with a M: F ratio of 1.3:1. At the time of study, 63 children were already diagnosed with epilepsy and taking AED mono-therapy medication while 67 children were newly diagnosed cases with epilepsy and were started on AED monotherapy. Generalized tonic-clonic seizure was the most common type of seizure seen in 75 children (57.7%) followed by

partial seizure in 50 cases (38.5%). There were two children with myoclonic and another two with atonic seizure (1.5 % each) and one patient with absence seizure (0.8 %). Majority of the children (n=66) in our study were on CBZ (50.8%) followed by VPA (n=55, 42.3%). There were four children on Phenytoin, another four on Phenobarbitone (3.1% each) and one child on Oxycarbazepine (0.8%). The mean values of the carotid IMT in the old cases and the newly diagnosed cases were 0.41 mm (± 0.11) and 0.38 mm (± 0.11), respectively. The mean values of carotid IMT in the male and female study population were 0.41 mm (± 0.11) and 0.43 (± 0.09), respectively which were not statistically significant.

On comparing the mean values of cIMT in different age groups as shown in Table 1, we observe that the increase in the thickness of carotid intima media was significantly increased with increase in age.

Table 1: Values of the mean cIMT in different age group.

Age group (years)	N	Mean IMT 1(mm)	SD 1	Mean IMT 2 (mm)	SD 2	Mean IMT 3 (mm)	SD 3
1-4	19	0.311	0.088	0.311	0.099	0.342	0.112
5-9	34	0.356	0.093	0.382	0.103	0.394	0.099
10-14	45	0.420	0.089	0.440	0.105	0.431	0.089
≥ 15	32	0.446	0.100	0.459	0.090	0.464	0.094
Total	130	0.394	0.104	0.411	0.111	0.416	0.103
F value		11.62		11.1		7.4	
df		3		3		3	
P value	45	0.00**		0.00**		0.00**	

** Significant at 0.01 level

Table 2: Mean Value of cIMT with duration of AED.

Duration (yrs)	N	Mean IMT 1	SD 1	Mean IMT 2	SD 2	Mean IMT 3	SD 3
0	67	0.37	0.09	0.38	0.11	0.40	0.10
0.25-1	16	0.39	0.07	0.39	0.08	0.42	0.07
1-2	13	0.42	0.10	0.45	0.11	0.44	0.11
2.1-3	14	0.41	0.10	0.43	0.11	0.42	0.13
>4	20	0.44	0.14	0.48	0.12	0.48	0.11
Total	130	0.39	0.10	0.42	0.11	0.43	0.10
F value		2.26		3.81		1.51	
Df		4		4		4	
P value		0.07		0.01*		0.02*	

*Significant at 0.05 level

Table 3: Mean value of cIMT for groups on different AED.

	N	Mean IMT 1 (mm)	SD 1	Mean IMT 2 (mm)	SD 2	Mean IMT 3 (mm)	SD
Valproic Acid	55	0.38	0.10	0.38	0.10	0.39	0.10
Carbamazepine	66	0.41	0.10	0.44	0.11	0.44	0.09
Phenytoin	4	0.40	0.12	0.44	0.16	0.40	0.14
Phenobarbitone	4	0.23	0.05	0.23	0.05	0.35	0.13
Total	129	0.39	0.10	0.41	0.11	0.41	0.10
F value		5.64		7.75		4.2	
P value		0.00**		0.00**		0.01*	

** Significant at 0.01 level, *Significant at 0.05 level

Table 4: Atherogenic indices of old and new cases.

	New		Old		t	df	p value
	Mean	SD	Mean	SD			
TC1/HDL1	2.27	1.35	2.57	1.70	-1.13	128	0.26
TC2/HDL2	2.15	1.04	2.43	1.48	-1.24	128	0.22
TC3/HDL3	1.94	0.84	2.18	1.16	-1.35	128	0.18
LDL1/HDL1	1.52	0.65	1.59	0.66	-0.57	128	0.57
LDL2/HDL2	1.55	0.62	1.63	0.76	-0.70	128	0.49
LDL3/HDL3	1.49	0.56	1.52	0.61	-0.36	128	0.72

When the values of cIMT were compared with the duration of intake of AED, it was observed that the values had increased on subsequent follow-up visits as shown in Table 2, and these values of cIMT were significantly increased with the increase in the duration of AED monotherapy. The values of carotid IMT in patients taking different AED are shown in Table 3. These values were significantly high in patients on CBZ and Phenytoin and this increase was significant in the subsequent follow-up visits. The serum cholesterol levels of the children already on anti-epileptic medications were found to be statistically significantly higher than the newly diagnosed children before the start of the anti-epileptic therapy. In both the CBZ and VPA prescribed group, the levels of serum cholesterol, LDL-C, HDL-C were significantly increased from the baseline when measured on follow-up. However, there was no difference seen in the levels of VLDL with any of the prescribed drugs with time.

The groups receiving Phenytoin and Phenobarbitone showed no statistically significant changes in the levels of the lipid profiles. The atherogenic indices of the newly diagnosed patients, taken as controlled, were comparable to those children who were already on long term anti-epileptics (Table 4). The atherogenic indices of the children taking any of the four anti-epileptic drugs were not statistically significant on follow up.

DISCUSSION

A total of 130 patients were analyzed in our study which was comparable to Kumar et al, Eiris et al in 1995 and Naithani et al.¹²⁻¹⁴ The gender distribution in our study comprises 57% males and 43% females; with a male: female ratio of 1.3:1. This was comparable to the gender distribution in other studies.^{15,16} The most common types of seizures encountered in our study were generalized tonic-clonic seizure and partial seizures which were seen in 58% and 38% of our patients, respectively.

This finding was similarly seen in other studies.^{12,15} In our study, the most commonly used AED was CBZ, similar to what was used by Ropper et al comprising 51% of our study population.⁷ This was similarly found in other studies where the number of patients on CBZ was comparable.^{13,17,18} VPA (42.3 %) was the second most

commonly used anti-epileptic drug, which is comparable to the number of cases seen in other studies.^{13,17} In present study it was observed that the mean values of cIMT in the controls were 0.38 mm±0.1 mm, which is comparable with the studies done by Mieczyslaw et al, Zhu et al and Dawson et al.¹⁹⁻²¹ The thickness of cIMT was not significantly increased in patients receiving CBZ and VPA as compared to controls. This value was comparable to other studies.¹⁹⁻²¹ However, there was a significantly higher value of cIMT in patients taking Phenytoin and Phenobarbitone as compared to the control group and patients on VPA and CBZ. This could be explained due to the older age group that was taking Phenytoin and Phenobarbitone. We also observed these similar findings; that with increasing age, the values of cIMT were increased as well.

This was similarly observed in a study conducted by Savitha et al and Webber et al.^{22,23} Amongst the biochemical parameters, we found that children who were taking CBZ had an increase in their total cholesterol, serum LDL and serum HDL levels and these findings were comparable to that observed by Chuang et al and Kantoush et al.^{24,25} Similarly, we observed that children, who were on VPA had an increase in their serum cholesterol, HDL and LDL levels which was comparable to the study done by Verrotti et al and a decrease in the levels of triglycerides on follow-up which was also similar to the findings done by Kantoush et al.^{26,25} The levels of VLDL did not significantly vary as the study progressed which was comparable to other studies.^{13,18} The atherogenic indices calculated for any of the four drugs were not significant, which was comparable to the study conducted by Eiris et al and Tekgul et al.^{18,27}

ACKNOWLEDGEMENTS

Authors would like to thank Dr. VMS Jaswal, Associate Professor, Department of Biochemistry, Indira Gandhi Medical College, for his help and contribution in the measurement and calculation of the biochemical parameters.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

- Johnston MV. Seizures in Childhood. In Kliegman R, Behrman R, Jenson H, Stanton B editors. Nelson textbook of pediatrics. Edition 19. WB Saunders; Philadelphia; 1993.
- Muuronen A, Kaste M, Nikkila EA. Mortality from ischemic heart disease among the patient using anticonvulsant drugs. *BMJ.* 1985;291:1481-3.
- Tumer L, Serdaroglu A, Hasanoglu A, Biberoglu G, Aksoy E. Plasma homocysteine and lipoprotein (a) levels as risk factors for atherosclerotic vascular disease in epileptic children taking anticonvulsants. *Acta Paediatr.* 2002;91:923-6.
- Strong JP, Zieske AW, Malcom GT. Lipoproteins and atherosclerosis in children: an early marriage?. *Nuts Metab Cardiovasc Dis.* 2001;11:16-22.
- Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracey RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med.* 1998;338:1650-6.
- Bots ML, Hoes AW, koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation.* 1997;96:1432-7.
- Ropper AH, Brown RH. Epilepsy and other seizure disorder. In Adam's and victor's principle of neurology. Edition 8. WB Mc Graw-Hill, USA. 2005:292-5.
- Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem.* 1974;20:470-5.
- Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. *Am J Med.* 1977;62:707-14.
- Schettler G and Nussel E. Method for triglyceride. *Aeb Med Soz Med Prav Med.* 1975;10:25-9.
- Friedewald WT, Levy RT, Fredrickson DS. Estimation of concentratin of low-density lipoprotein cholesterol without the use of preparative centrifuge. *Clin Chem.* 1989;22:417- 23.
- Kumar P, Tyagi M, Tyagi YK, Kumar A, Kumar A, Rai YK. Effect of Anticonvulsant Drugs on Lipid Profile In Epileptic Patients. *The Internet J Neurol.* 2004;3:1.
- Eiris JM, Castro-Gago M, Lojo S. Effect of long term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy. *Neurol.* 1995;45:1155-7.
- Naithani M, Chopra S, Somani BL, Singh RK. Studies on Adverse metabolic effects of antiepileptics and their correlation with blood components. *Current Neurobiol.* 2010;1:117-20.
- Mahmoudian T, Iranpour R, Messri N. Serum lipid levels during carbamazepine therapy in epileptic children. *Epilepsy Behav.* 2005;6:257-9.
- Yilmaz E, Doğan Y, Gürgöze MK, Gungor S. Serum lipid changes during anticonvulsive treatment, serum lipids in epileptic children. *Acta Neurol Belg.* 2001;101:217-20.
- Franzoni E, Govoni M, D'Addato S. Total Cholesterol, High-density lipoprotein cholesterol, and triglycerides in children receiving antiepileptic drugs. *Epilepsia.* 1992;33:932- 5.
- Eiris J, Novo-Rodriquez MI, Del Rio M, Meseguer P, Castro-Cago M. The effects on lipid and apolipoprotein serum levels of long-term carbamazepine, valproic acid, and Phenobarbital therapy in children with epilepsy. *Epilepsy Res.* 2000;41:1-7.
- Mieczysław L, Trelewicz J, Zbigniew W. Intima media thickness and arterial elasticity in hypertensive children: controlled study. *Pediatr Nephrol.* 2004;19:767-74.
- Zhu W, Huang X, He J, Li M, Neubauer H. Arterial intima-media thickening and endothelial dysfunction in obese Chinese children. *Eur J Pediatr.* 2005;164:337-44.
- Dawson JD, Sonka M, Blecha MB, Lin W, Davis PH. Risk factors associated with aortic and carotid intima-media thickness in adolescents and young adults. *J Am Coll Cardiol.* 2009;53:2273-79.
- Savitha MR, Sandeep B. The study of lipid profile, diet and other cardiovascular risk factors in children born to parents having premature ischemic heart disease. *Indian J Community Med.* 2011;36:291-5.
- Webber LS, Srinivasan SR, Wattigney WA, Berenson GS. Tracking of serum lipids and lipoproteins from childhood to adulthood: The Bogalusa Heart Study. *Am J Epidemiol.* 1991;133:884-99.
- Chuang YC, Chuang YH, Lin TK, Lu CH, Chang WN, Chen SD et al. Effects of long term anti-epileptic drug monotherapy on vascular risk factors and atherosclerosis. *Epilepsia.* 2012;53:120-8.
- Kantoush MM, El-Shahawy AK, Sokker SS, Serag HR. Effects of treatment with antiepileptic drugs on serum lipid profile in epileptic children. *Alex. J Pediatr.* 1998;12:153-8.
- Verrotti A, Di Marco G, La torre R, Pellicia P, Chiarelli F. Non-alcoholic liver disease during Valproate therapy. *European J Pediatr.* 2009;168:1391-4.
- Tekgul H, Demir N, Gokben S. Serum lipid profile in children receiving antiepileptic drug monotherapy: is it atherogenic?. *J Pediatr Endocrinol Metab.* 2006;19:1151-5.

Cite this article as: Ksoo R, Sharma R, Kaushal RK, Jhobta A. The effects on carotid artery intima-media wall thickness and development of atherosclerosis in children on anti-epileptic drug monotherapy. *Int J Contemp Pediatr* 2017;4:1369-73.