Child Neurology Open
Volume 3: 1-6

DOI: 10.1177/2329048X16658364
cno.sagepub.com
SAGE

Assessment of Subclinical Pancreatitis in Epileptic Children With Different Treatment Modalities

Doa Mohamed Mahrous, MD[1], Gehan Lotfy Abdel Hakeem, MD[1], Reem Abdel Salam Abdel Aziz, MD[1], and Aliaa Monir Higazi, MD[2]

Abstract

Acute pancreatitis differ in pediatrics and adults. Drug-induced pancreatitis is one of the common causes of pancreatitis in children. This case–control study aimed to assess subclinical pancreatitis in patients with epilepsy treated with different drug regimens. Eighty known patients with epilepsy were enrolled. Forty patients were treated with monotherapy (group I) and 40 were treated with multitherapy (group II) regimens. Twenty age- and sex-matched healthy children were enrolled as control (group III). Serum lipase and amylase were assayed in all included children. Significant differences were found between groups I and III and between groups II and III regarding serum amylase and lipase ($P < .001$ for all). Significant difference were found between groups I and II ($P = .024$) and between groups II and III ($P = .01$) regarding pancreatic duct and body diameters. Significant difference were found between patients with controlled and uncontrolled fits regarding serum amylase ($P = .008$). In conclusion, subclinical pancreatitis can complicate the treatment with different antiepileptic regimens.

Keywords

subclinical pancreatitis, epilepsy, antiepileptic regimens

Received January 19, 2016. Received revised May 26, 2016. Accepted June 03, 2016.

Pancreatitis is defined as the histological presence of inflammation within the parenchyma of the pancreas.[1] Elevations in serum amylase and lipase are the most common biochemical determinants of pancreatitis.[2] In pediatric studies, the sensitivity of the amylase test in diagnosing pancreatitis has ranged from 50% to 85%. Lipase was only marginally more sensitive than amylase in most studies.[3]

Epilepsy is defined as a condition characterized by recurrent seizures.[4] Once diagnosis of epilepsy has been established, pharmacotherapy is usually indicated.[5]

The link between administering sodium valproate and pancreatitis has been widely documented[6]; however, recent studies have revealed that there is a similar risk of acute pancreatitis in patients treated with other antiepileptic drugs because of the estimated risk associated with valproic acid.[7] The purpose of this study was to assess the levels of serum lipase and serum amylase in children treated with antiepileptic drugs.

Participants and Methods

Patients

One hundred participants were enrolled in this study from November 2012 to July 2013. Eighty of them were known patients with epilepsy recruited to the pediatric neurology clinic in Minia Obstetrics and Children's University hospital

[1] Pediatric Department, Faculty of Medicine, Minia University Children's Hospital, Minia University, Minya, Egypt
[2] Clinical Pathology Department, Faculty of Medicine, Minia University Hospital, Minya, Egypt

Corresponding Author:
Gehan Lotfy Abdel Hakeem, MD, Pediatric Department, Faculty of Medicine, Minia University Children's Hospital, Minia University, El-Menia, Minya 61111, Egypt.
Email: gehanlotfy72@yahoo.com

Table 1. Comparison Between the Studied Groups Regarding Some Demographic, Radiologic, and Laboratory Data.

				P Value		
	Group I (n = 40)	Group II (n = 40)	Group III (n = 20)	I Versus II	I Versus III	II Versus III
Mean age, months	50 ± 3.5	61.89 ± 2.4	57.4 ± 3.1	.21	.425	.266
Sex						
Female	19 (47.5%)	24 (60%)	13 (65%)	.108	.146	.890
Male	21 (52.5%)	16 (40%)	7 (35%)			
Family history						
Positive	15 (37.5%)	17 (42.5%)	0 (0%)	.34	.486	.729
Negative	25 (62.5%)	23 (57.5%)	20 (100%)			
Pancreatic duct diameter, mL	1.37 ± 0.56	1.64 ± 0.6	1.28 ± 0.33	.024	.542	.016
Pancreatic body diameter, cm	1.11 ± 0.25	1.03 ± 0.24	0.95 ± 0.13	.021	.566	.015
Parenchyma						
Homogeneous	33 (78.6%)	32 (84.2%)	20 (100%)	.519	.025	.061
Nonhomogeneous	9 (21.4%)	6 (15.8%)	0 (0%)			
Echo						
Echogenic	32 (76.2%)	33 (86.8%)	20 (100%)	.223	.017	.090
Hypoechogenic	10 (23.8%)	5 (13.2%)	0 (0%)			
Amylase, IU/L	330.97 ± 17.7	323.52 ± 0.13	53.3 ± 4.58	.711	<.001	<.001
Lipase, IU/L	312.73 ± 36.3	355.21 ± 22.3	38.1 ± 23.21	.365	<.001	<.001

with an age range of 2 to 12 years, with at least 6 months' duration of therapy included and classified as follows:

Group I: Included 40 patients treated with monotherapy of traditional or second-generation antiepileptic drug.

Group II: Included 40 patients with epilepsy treated with either traditional multitherapy or multitherapy (antiepileptic drugs), where 1 of them at least is a second-generation antiepileptic drug.

Another 20 age- and sex-matched healthy children served as controls.

All enrolled patients were treated by antiepileptic drugs according to the National Institute for Health and Care Excellence guidelines,[8] including the recommendations for drug therapy of different types of seizures.

The drug dosages used for included patients (groups I and II) were as follow:

sodium valproate 20 to 60 mg/kg/d in 2 to 3 divided doses, carbamazepine 10 to 20 mg/kg/d, clonazepam (<1 year: 500 μg-1 mg/d, 1-5 years: 1-3 mg/kg/d, and 5-12 years: 3-6 mg/kg/d) twice a day, ethosuximide 20 to 40 mg/kg/d (twice a day), lamotrigine (when with sodium valproate: 1-5 mg/kg/d while without sodium valproate: 5-15 mg/kg/d) once or twice daily, levetiracetam: 10 to 60 mg/kg/d (twice a daily), and oxacarbamazepine: 10 to 46 mg/kg/d. Patients with underlying causes or symptoms of acute pancreatitis were excluded.

Methods

All participants were subjected to a thorough history taking, stressing on age, gender, age of onset of convulsions (in months), character of convulsions, duration of treatment with antiepileptic drugs, convulsions controlled or not, and family history of convulsions and also complete general and full neurological examinations. Ultrasonographic examination was done in all participants. Laboratory investigations included serum lipase and serum amylase by quantitative colorimetric assay.

Sampling

Two milliliter of venous blood on plain plastic tubes left to be clotted in the incubator and centrifuged at 2500*g* for 10 minutes. Separated serum was divided into 2 adequate samples and stored at (2°C-8°C) for maximum 4 days until the time of lipase and amylase assay.

Normal Values (in Children)

Amylase: serum—up to 82 U/L and lipase: serum—up to 60 U/L.[9]

Statistical Analysis

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 20. Descriptive statistics were done for numerical data by mean and standard deviation while for categorical data using number and percentage. For quantitative variables, analyses were done using 1-way analysis of variance for normally distributed quantitative data between more than 3 groups and post hoc test for each of the 2 groups. Independent sample (*t*) test for quantitative data was used between 2 groups. Chi-square test used for qualitative data between groups. The level of significance was taken at *P* value <.05.

Results

Eighty known patients with epilepsy were included in this study classified as 2 groups. In group I, 19 (47.5%) boys and 21 (52.5%) girls were included, and the mean age was 50 ± 3.5 months, whereas in group II, 24 (60%) boys and 16 (40%) girls were included, and the mean age was 61.9 ± 2.4 months (Table 1).

Table 2. Correlation Between Serum Amylase and Serum Lipase Levels in Relation to the Duration of Treatment in Months.

Duration of Treatment, months	*r*	*P* Value
Serum amylase level, IU/L	.124	.273
Serum lipase level, IU/L	.181	.107

Table 3. Comparison Between Serum Amylase and Serum Lipase Levels in Relation to the Fate of Convulsions.

	Controlled (n = 70)	Not Controlled (n = 10)	*P* Value
Mean serum amylase, IU/L	306.32 ± 184.28	475.2 ± 175.28	.008
Mean serum lipase, IU/L	344.4 ± 506.09	252.5 ± 143.78	.527

No significant difference was found in both study (I and II) and control (III) groups regarding age, sex, and family history (Table 1). Ultrasonographic examination shows significant difference between groups I and II regarding pancreatic duct and body diameters ($P = .024$ and .021, respectively). Echogenic changes and homogenous parenchyma were found in group I, compared to control group ($P = .017$ and 0.025, respectively) (Table 1).

Comparing both the studied groups, there were significant differences in the duration of therapy ($P = .003$) (Table 2), whereas no significant differences were observed in the type of convulsion ($P = .59$), electroencephalography changes ($P = .59$), and the fate of convulsions ($P = .87$).

Highly significant differences were found between both studied groups and controls regarding serum amylase ($P < .001$) and lipase ($P < .001$), whereas no significant differences were found when both studied groups were compared ($P = .7$ for serum amylase and .37 for serum lipase) (Table 1).

Serum amylase was significantly elevated in patients with uncontrolled fits ($P = .008$), whereas there was no significant difference in the fate of convulsion regarding serum lipase ($P = .53$) (Table 3, Figure 1).

The serum amylase level was highest in patients with focal fits (376.6 ± 19.03) and lowest in those with tonic convulsions (306 ± 179.8), whereas serum lipase was highest in patients with tonic convulsion (932.4 ± 110.8) and lowest in patients with focal convulsions (143.8 ± 72.9; Figure 2).

The incidence of generalized tonic–colonic convulsions was higher in group I (76.2%) than in group II (68.4%), whereas the incidence of focal convulsions was lower in group I (11.9%) than in group II (15.8%).

The incidence of partial seizures with secondary generalization was lower in group I (2.4%) compared to group II (7.9%). Absence seizures were 2.4% for group I and nil (0%) for group II.

In group I, 30 patients were treated with sodium valproate, 28 (93.3%) of them were responsive to fits control, whereas levetiracetam was used in 10 patients with 90% fit control. In group II, 35 patients were treated by sodium valproate, and in 94.3% of these patients, it was controlled. Nineteen patients were treated with oxcarbamazepine, 18 (94.7%) of them showed control, whereas 21 patients were treated with carbamazepine, 19 (90.5%) of them showed control (Table 4, Figure 1). No significant correlation between both serum amylase and lipase and the duration of treatment with antiepileptic drugs (Table 2). Serum lipase was the highest with Sodium valproate treatment and the lowest with Oxcarbamazepine treatment while serum amylase was the highest with Carbamazepine treatment and the lowest with Levetiracetam treatment (Figure 3).

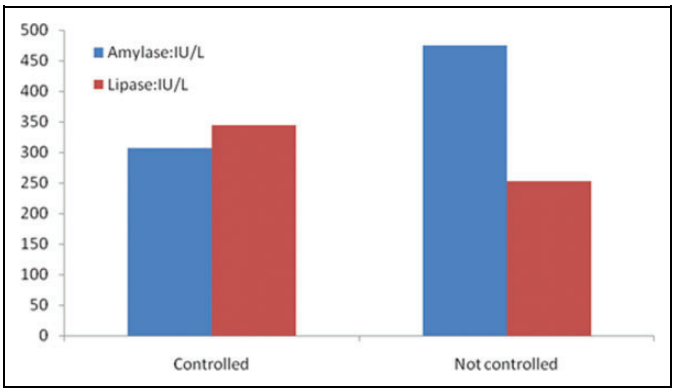

Figure 1. Comparison between serum amylase and serum lipase levels in relation to the fate of convulsions.

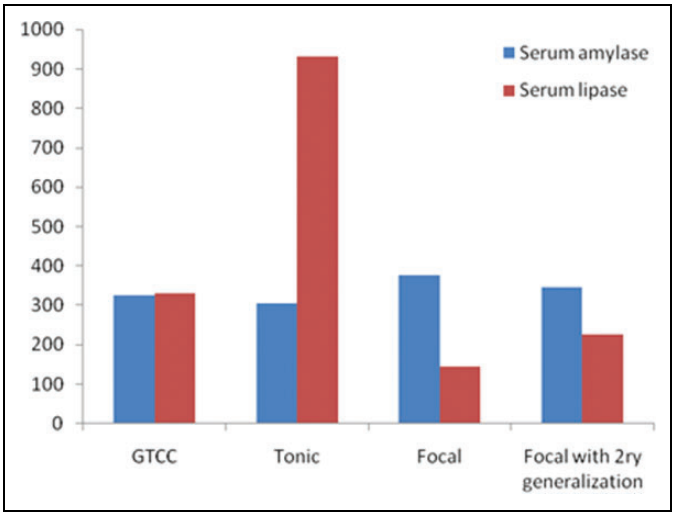

Figure 2. Comparison between serum amylase and serum lipase levels in relation to the type of convulsions.

Discussion

Epilepsy is defined as a condition characterized by recurrent seizures.[4] Once the diagnosis of epilepsy had been established, pharmacotherapy is indicated.[5]

Pancreatitis is a sudden inflammation of the pancreas. It can be associated with severe complications and high mortality despite treatment.[10] In the present study, subclinical pancreatitis had been proved anatomically in the absence of clinical

Table 4. Types of Antiepileptic Drugs Used in Relation to the Outcome of Fits.

Antiepileptic Drugs Used		Controlled Fits	Uncontrolled Fits
Group I	Sodium valproate (n = 30)	28 (93.3%)	2 (6.7%)
	Levetiracetam (n = 10)	9 (90%)	1 (10%)
Group II	Carbamazepine (n = 21)	19 (90.5%)	2 (9.5%)
	Oxacarbamazepine (n = 19)	18 (94.7%)	1 (5.3%)
	Sodium valproate (n = 35)	33 (94.3%)	2 (5.7%)

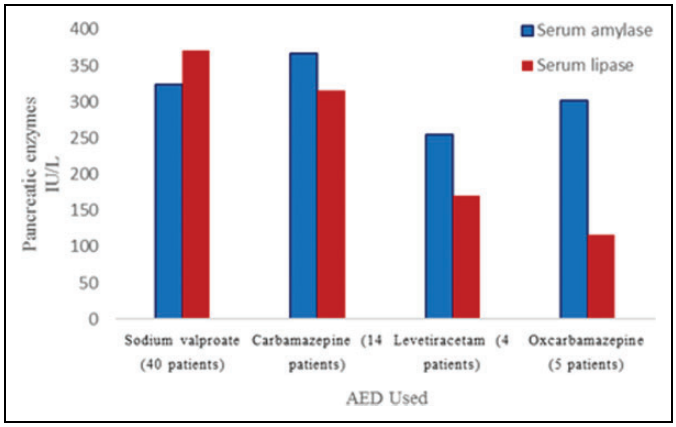

Figure 3. Comparison between serum amylase and serum lipase levels in relation to the treatment with some antiepileptic drugs.

signs. Ultrasonography had shown widening in pancreatic body and duct diameters, which is more in patients treated with multidrug regimen compared to single-drug regimen patients and the control group. Most of the patients with pancreatitis have a dilated pancreatic duct as compared to age-matched control, and pancreatic duct diameter might be more valuable than the diameter of pancreatic body for evaluating pancreatitis.[11]

The link between administering sodium valproate and pancreatitis had been widely documented.[6] Recent studies revealed similar risk of acute pancreatitis in patients treated with other antiepileptic drugs because of the estimated risk associated with sodium valproate therapy.[7] Our study is the first to discuss this issue in pediatric patients. As known, valproic acid has a direct cellular toxic effect due to the free radicals[12] and carnitine depletion can play an important role in pancreatic injury.[13] Other antiepileptic drugs can also contribute to the creation of free radicals[14] and carnitine depletion.[15] Elevations in serum amylase and lipase are the most common biochemical determinants of pancreatitis.[2]

In the current study, there were highly significant differences between groups I versus III and groups II versus III regarding serum amylase and lipase levels ($P < .001$ for all). These results agree with that of Leena et al[16] where all patients (100%) had an elevated serum lipase level and 61% with elevations were in both lipase and amylase levels. Phenytoin, phenobarbital, or carbamazepine did present higher levels of lipase and pancreatic amylase than the control group, and the difference was significant. The hepatic enzyme inducer nature of most antiepileptic drugs could be a strong factor for elevation of pancreatic lipase and amylase levels.[7] The alteration in the lipid composition and the permeability of the plasmatic membranes by antiepileptic inducer drugs encourages membrane and cytosolic enzymes to be released into the extracellular medium and enter the circulatory flow.[17] The pancreas contains abundant gamma-glutamyl transferase enzyme. Elevated gamma-glutamyl transferase activity was detected in the group of patients treated with phenytoin, phenobarbital, and carbamazepine. This type of action can help to explain the strong correlation between gamma-glutamyl transferase serum activities and pancreatic amylase in patients treated with phenytoin, phenobarbital, and carbamazepine.[18]

About the numbers of antiepileptic drugs used, the authors found significant differences in the levels of serum amylase and lipase between group I (monotherapy of antiepileptic drugs) and group III (control), where the P value (<.001) between group II (polytherapy of antiepileptic drugs) versus group III ($P < .001$) agree with the results obtained by Hermida Ameijeiras et al,[19] and the group of patients treated with phenytoin, phenobarbital, or carbamazepine either alone or in combination presented higher lipase and pancreatic amylase levels than the control group, and the differences were statistically significant. The evidence of subclinical chemical pancreatitis is more in patients with multiple drug therapy regimen and in patients with uncontrolled fits, suggesting the synergistic action of the antiepileptic drugs in inducing pancreatic injury, keeping in mind that patients with uncontrolled fits were mostly treated with more than 1 antiepileptic drug.

In the current study, the authors have studied 80 epileptic children, 40 of them were treated with sodium valproate, all of them had subclinical pancreatitis and had elevated serum amylase and lipase levels. The World Health Organization 2010 reported that among 2749 reports of drug-associated acute pancreatitis between 1968 and 1993, valproic acid was the most frequently reported drug.[20] Also, in all of the case reports of valproic acid–induced acute pancreatitis, 75% occurred in the pediatric population.[21] As valproic acid is the most widely used antiepileptic drug in children,[22] it is probably the most frequent cause of drug-induced pancreatitis[2] followed by different other antiepileptic drugs. The duration of treatment of epilepsy with either single-drug regimen or multiple drug regimens had no correlation with either serum amylase or lipase levels.

Pancreatitis had the highest risk during the first year of treatment in a case series of 11 children who had valproic acid–induced acute pancreatitis. Children with a history of drug allergies, that is, rashes were at increased risk, whereas treatment duration was not considered a risk factor.[23] Acute pancreatitis caused by valproic acid may be due to some forms of idiosyncratic complications rather than long-term cumulative drug or age-related actions.[7]

Also, the direct toxic effect of antiepileptic drug due to the free radicals[12] and the depletion of carnitine may have played an important role in subclinical pancreatic injury rather than the long-term drug exposure.[13-15]

Serum amylase and lipase levels were not significantly differ regarding the type of antiepileptic drug (traditional or second-generation antiepileptic drug). There is a similar risk of acute pancreatitis regardless of the drug classification.[7,19]

Conclusion

Subclinical pancreatitis can complicate the treatment with different antiepileptic regimens in children having epilepsy, with more chances with multiple than with single-drug therapy. It is not affected by the duration of therapy or the generation of antiepileptic drugs used.

Recommendations

Whatever the antiepileptic regimen used, serum amylase and lipase levels should be assayed regularly in epileptic patients for their greater risk of developing overt clinical pancreatitis.

Limitation of the Study

Serum antiepileptic drug levels were not available because the patients were collected randomly from the pediatric neurology outpatient clinic. Also, no preexisting radiographic criteria for pancreatitis for studied patients were available.

Acknowledgments

This research was performed in the Pediatric Neurology Unit at Minia University Children's Hospital in Minya, Egypt. The authors thank the nurse staff for recording clinical data of included patients.

Author Contributions

DMM conceived the study. GLA, RAA, and AMH participated in its design and coordination. GLA and RAA provided key technical guidance and drafted the manuscript. DMM and AMH critically revised the manuscript for important intellectual content.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed that no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

The institutional review board for Human Research of Faculty of Medicine-Minia University approved this study. All study participants provided written informed consent.

References

1. Bradley EL III. A clinically based classification system for acute pancreatitis: summary of the International Symposium on Acute Pancreatitis. *Arch Surg*.1993;128(5):586-590.
2. Bai HX, Ma MH, Orabi AI, et al. Novel characterization of drug-associated pancreatitis in children. *J Pediatr Gastroenterol Nutr*. 2011;53(4):423-428.
3. Park A, Latif SU, Shah AU, Tian J, Werlin S, Hsiao A. Changing referral trends of acute pancreatitis in children: a 12-year single-center analysis. *J Pediatr Gastroenterol Nutr*. 2009;49(3): 316-322.
4. Guidelines for epidemiologic studies on epilepsy. Commission on epidemiology and prognosis, international league against epilepsy. *Epilepsia*. 1993;34(4):592-596.
5. Perucca E. Marketed new antiepileptic drugs: are they better than old-generation agents? *Ther Drug Monit*. 2002;24(1): 74-80.
6. Lancashire RJ, Cheng K, Langman MJ. Discrepancies between population based data and adverse reaction reports in assessing drugs as causes of acute pancreatitis. *Aliment Pharmacol Ther*. 2003;17(7):887-893.
7. Norgaard M, Jacobsen J, Ratanajamit C, et al. Valproic acid and risk of acute pancreatitis: a population-based case-control study. *Am J Ther*. 2006;13(2):113-117.
8. National Institute for Health and Care Excellence (NICE). Epilepsy diagnosis and management. Web site. https://www.nice.org.uk/guidance/cg137/chapter/1-guidance. 2012. Updated 2016.
9. Lott JA, Lu CJ. Lipase isoforms and amylase isoenzyme: assays and application in the diagnosis of acute pancreatitis. *Clin Chem*. 1991;37(3):361-368.
10. Lucille S. Acute pancreatitis. *Am J Nurs*. 1935:35(12):1157-1161.
11. Chao HC, Lin SJ, Luo CC. Sonographic evaluation of the pancreatic duct in normal children and children with pancreatitis. *J Ultrasound Med*. 2000;19(11):757-763.
12. Pellock JM, Wilder BJ, Deaton R, Sommerville KW. Acute pancreatitis coincident with valproate use: a critical review. *Epilepsia*. 2002;43(11):1421-1424.
13. Moreno FA, Macey H, Schreiber B. Carnitine levels in valproic acid treated psychiatric patients: a cross-sectional study. *J Clin Psychiatry*. 2005;66(5):555-558.
14. Hamed SA, Abdellah MM, El-Melegy N. Blood levels of trace elements, electrolytes, and oxidative stress/antioxidant systems in epileptic patients. *J Pharmacol Sci*. 2004;96(4): 465-473.
15. Rodríguez Segade S, de la Peña CA, Tutor JC, et al. Carnitine deficiency associated with anti convulsant therapy. *Clin Chim Acta*. 1989;181(2):175-181.
16. Leena K. Etiology and outcome of acute pancreatitis in infants and toddlers. *J pediatr*. 2008;152(1):106-110.

17. Nemesanszky E. Enzyme tests in hepatobiliary disease. In: Moss DW, Rosalki SB, eds. *Enzyme Tests in Diagnosis*. London, UK: Arnold; 1996: 25-59.
18. Tutor Crespo MJ, Hermida-Ameijeiras J, Tutor Valcarce JC. A study of some indirect biochemical markers in the evaluation of enzyme induction caused by antepileptic drugs. *Rev Neurol*. 2002; 35(8):711-716.
19. Hermida Ameijeiras J, Tutor Crespo MJ, Tutor Valcarce JC. Lipase and total amylase and its isoenzymes as markers of pancreatic injury in patients treated with antiepileptic drugs. *Farm Shop*. 2007;31(5):303-306.
20. World Health Organization. Epilepsy: Key facts. 2012. Web site. www.who.int/mediacentre/factsheets/fs999/en. Updated 2016.
21. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug induced acute pancreatitis: an evidence based review. *Clin Gastroenterol Hepatol*. 2007;5(6):648-661.
22. José-Guevara Campos J, González-Guevara L, Vacaro-Bolívar L. Acute pancreatitis associated to the use of valproic acid Arq. *Neuro Psiquiatr*. 2009;67(2-B):513-515.
23. Sinclair DB, Berg M, Breault R. Valproic acid-induced pancreatitis in childhood epilepsy. *J Child Neurol*. 2004;19(7):223-227.