*Research Article / Araştırma Makalesi*

# Investigation of Apelin Level and Oxidative Damage in Children Diagnosed with Epilepsy for the First Time

## İlk Kez Epilepsi Tanısı Konulmuş Çocuklarda Apelin Düzeyinin ve Oksidatif Hasarın Araştırılması

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**Background:** Epilepsy disease, which negatively affects 65 million people around the world, can be seen in all age groups regardless of gender. Disease is known throughout the history of human disease, although the mechanism is still unknown. In this study, it is aimed to investigate of apelin and oxidative stress levels in children with epilepsy.
**Materials and Methods:** Children with epilepsy (aged 0-16) who had been diagnosed with epilepsy and did not start treatment were included in the study. This study included control group healthy normal children (n=28) and children with epilepsy group (n=28), totally 56 children were included. Blood samples were removed for apelin, advanced protein oxidation product (AOPP) and DNA damage marker 8-Hydroxy 2-Deoxyguanosine (8-OHdG) levels analyses by ELISA method.
**Results:** Apelin level in generalized type epilepsy was lower than the control group and the complicated febrile group ($p<0.05$). It has been found that the number of epilepsy seizures is more common in the generalized type epilepsy ($p<0.05$). While the number of seizures decreased due to the increase in apelin ($p=0.05$; $r=-0.260$), it increased due to the increase in AOPP ($p=0.05$; $r=0.264$). AOPP was higher in focal type epilepsy than control group.
**Conclusions:** Consequently; 1) Apelin reduced the number of seizures by preventing oxidative DNA damage, 2) Increased the number of seizures by the AOPP increase, 3) As the age rises, the number of seizures has been determined to lower due to decreased in AOPP level.

**Key Words:** Epilepsy, Apelin, Oxidative stress, 8-OHdG, AOPP

**ÖZ.**

**Amaç**: Dünya genelinde 65 milyon kişiyi olumsuz etkileyen epilepsi hastalığı, cinsiyet ayrımı olmaksızın tüm yaş gruplarında görülebilmektedir. Mekanizması henüz bilinmemekle birlikte, hastalık insan hastalıklarının tarihi boyunca bilinmektedir. Bu çalışmada epilepsili çocuklarda apelin ve oksidatif stres düzeylerinin araştırılması amaçlanmıştır.
**Materyal ve Metod:** Çalışmaya epilepsi tanısı konan ve tedaviye başlamamış epilepsili (0-16 yaş) çocuklar dahil edildi. Çalışma, kontrol grubu sağlıklı normal çocuklar (n=28) ve epilepsili çocuklar (n=28) olmak üzere toplam 56 çocukta yapıldı. Apelin, ileri protein oksidasyon ürünü (AOPP) ve DNA hasar markeri 8-Hidroksi 2-Deoksiguanozin (8-OHdG) seviyeleri analizleri için ELISA yöntemi ile kan örnekleri alındı.
**Bulgular:** Jeneralize tip epilepside apelin düzeyi kontrol grubuna ve komplike ateşli gruba göre daha düşüktü ($p<0.05$). Epilepsi nöbet sayısının jeneralize tip epilepside daha fazla olduğu bulundu ($p<0.05$). Apelin artışına bağlı olarak nöbet sayısı azalırken ($p=0.05$; $r=-0.260$), AOPP artışına bağlı olarak arttı ($p=0.05$; $r=0.264$). AOPP, fokal tip epilepside kontrol grubuna göre daha yüksekti.
**Sonuç:** Sonuç olarak; 1) Apelin, oksidatif DNA hasarını önleyerek nöbet sayısını azalttı, 2) AOPP artışı ile nöbet sayısını artırdı, 3) Yaş arttıkça AOPP düzeyindeki azalma nedeniyle nöbet sayısının azaldığı belirlendi.

**Anahtar kelimeler:** Epilepsi, apelin, oksidatif stres, 8-OHdG, AOPP

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**Received / Geliş tarihi:** 14.10.2021

**Accepted / Kabul tarihi:** 24.11.2021

**DOI:** 10.35440/hutfd.1006598

*This study consists of Vedat AKSU's master degres's thesis data.*
*This study was presented as a summary presentation at the 4th International Congress of Turkish Neuroendocrinology Society (26-28 November 2020, Istanbul).*

## Introduction

Apelin is a hormone secreted from the adipose tissue and a neuropeptide found in the human brain could have a role in the occurrence mechanism of epilepsy (1, 2). It has been reported that apelin and the apelin receptor (APJ) play an active role both in peripheral tissues and the central nerve system (CNS) (3). An increase of the apelin expression in the lithium-pilocarpine epilepsy model and temporal neocortex in the hippocampus and surrounding cortex structures was detected (4). The molecular mechanism of this increase cannot be totally explained.

Epilepsy is the fourth most common neurological disorder, affecting 65 million people around the world (5). Epilepsy is defined by irregular electrical activities in the cerebral neurons, which start and end without an external factor, and which recur at least twice or have the risk of recurrence (6). Epilepsy can occur in every age group regardless of sex; in fact, it is estimated that there are 10.5 million patients globally under the age of fifteen. Although the cause of epilepsy is not understood completely, head traumas, bleedings, infection, stroke, anomalies and tumors in the brain structure, use of toxic substances, and some drugs are among the main reasons for its occurrence (7). It is also known that extrasynaptic events, cell loss, altered receptor production, anatomical changes at the cellular level, hyperstimulation in presynaptic termination, and neuropeptides that affect signal activity in the brain have a role in the occurrence mechanism of epilepsy (8). It has been reported that epileptic seizures may be affected by various endocrinological factors and should be considered in the clinical approach to an epileptic patient, especially in children (9). Many of the most recent studies have showed an increase in genotoxic and cytotoxic effects due to free oxygen radicals among patients with epilepsy, and the studies have revealed that epilepsy is a neurodegenerative disease. However, there is no study that examines whether apelin has a neuroprotective effect against damage induced by free oxygen radicals in these patients.

This study examined the correlations between epilepsy in children and apelin and oxidative stress parameters. Additionally, epilepsy types and the number of epileptic seizures were determined, as were their correlations with apelin and oxidative stress parameters.

## Materials and Methods

### *Participants and Study Design*

The study included individuals who consulted the Harran University Medical Faculty Research and Training Hospital Pediatric Neurology polyclinic and were subsequently diagnosed with either epilepsy (based on the International League Against Epilepsy (ILAE) Classification) or were determined to have a febrile seizure. Diagnosis and classification of epilepsy were determined by electroencephalogram (EEG). Individuals selected for the epilepsy group were newly diagnosed patients aged 0-16 years, who did not have any metabolic, genetic, or chronic disease. In addition, these individuals were taken the diagnosis of their first convulsion and they have not been treated yet by a physician. Their family members have reported that it was the first convulsion for these patients.

The epilepsy group consisted of twenty-two individuals (11 male, 11 female). The patients were divided into three groups based on the following epilepsy types: focal type (n=13), generalized type (n=7), and idiopathic generalized type (n=2). In addition, a complicated febrile group (n=6) was formed with four male and two female patients who had experienced a febrile attack for the first time and thus were at risk for epilepsy.

The control group was formed with children who did not have any metabolic and genetic diseases, and did not have an epileptic seizure, and who consulted the dermatology clinic. The control group included twenty-eight individuals (16 male, 12 female) who were regarded as healthy by the doctor and who did not have any chronic disease.

The approval of the Harran University Non-Interventional Clinical Studies Ethics Committee (Date:05/01/2017 Decision No: 17/01/19) was obtained to conduct the study.

### *Sample collection*

After the participants were informed about the study, their names, ages, bodyweights, and lengths were recorded. The number of seizures per month of children in the epilepsy group was recorded according to the notifications of the parents. Venous blood was taken from all individuals in the morning on an empty stomach. Blood samples were put in gel biochemistry tubes and centrifuged at 3500 rpm for 10 minutes in the biochemistry laboratory. The serum samples were put into Eppendorf tubes and kept at -80 ˚C until ELISA analyses were conducted.

### *Hormone analyses*

Apelin, AOPP, and 8-OH guanine analyses in the serum samples were made using commercial ELISA kits (USCN, China).

### *Statistical analyses*

The IBM SPSS Statistics 25.0 program was used for the statistical analyses. The suitability to normal distribution was assessed using the Shapiro-Wilk test. The independent t-test was used for binary comparisons of data with normal distribution in the statistical analyses. The Mann-Whitney U test was used for binary comparisons of data without normal distribution. The data with normal distribution were presented as mean±SE while the data without normal distribution were presented as median±SD. The analyses of correlations between the parameters were made with the Spearman's correlation test, and the statistical significance level was determined as $p<0.05$.

## Results

### *Participants*

General characteristics of the participants (age, BMI, gender) are presented in Table 1. It was determined that the distribution of gender, age, and BMI was similar between the control and epilepsy groups ($p$>0.05).

**Table 1.** General characteristics of the control and patient groups.

| | Control *(n=28)* | Epilepsy *(n=22)* | Complicated Febrile *(n=6)* | |
|---|---|---|---|---|
| | Median (min-max) | Median (min-max) | Median (min-max) | *p** |
| **Age** | 7 (2-14) | 6.5 (1-15) | 2 (1.56-5) | 0.274 |
| **BMI (kg/m²)** | 15 (12.82-30.94) | 16.0 (11.21-21.75) | 14.8 (7.81-17.24) | 0.939 |
| **Female** | 12 | 11 | 2 | 0.88 |
| **Male** | 16 | 11 | 4 | 0.88 |

*BMI; Body mass index*

**p values represent the results of comparison between the control and epilepsy groups.*

### *Serum AOPP, Apelin and 8-OHdG*

The serum 8-OHdG, apelin, and AOPP levels of each group are presented in Table 2.

**Table 2.** Comparison of mean serum 8-OHdG, apelin, and AOPP levels of the patient groups and the control group.

| | Control *(n=28)* | Epilepsy *(n=22)* | |
|---|---|---|---|
| | Mean (Std Error) | Mean (Std Error) | *p** |
| **Serum 8-OHdG** | 41.21 (2.65) | 43.61 (2.43) | 0.530 |
| **Serum Apelin** | 20.82 (0.61) | 19.30 (0.81) | 0.197 |
| **Serum AOPP** | 25.53 (0.34) | 26.01 (0.22) | 0.229 |

*8-OHdG; 8-hydroxy-2' -deoxyguanosine, AOPP; Advanced oxidation protein products.*

**p values represent the results of comparison between the control and epilepsy groups.*

As indicated, there were no statistically significant differences between the groups in terms of these parameters ($p$>0.05). Individuals (n=10) were randomly selected from the control group and comparisons were made to determine whether there was a difference in the serum AOPP, apelin, and 8-OHdG levels according to epilepsy type. The patient group was divided into two groups based on epilepsy type: focal (n=13) and generalized (n=7). Since the number of patients in the idiopathic generalized (n=2) type was small, these patients were not included in the comparisons between epilepsy types. Accordingly, statistical comparisons were made between the control, focal, generalized, and complicated febrile (n=6) groups. It was determined that the BMI values of the four groups were similar ($p$= 0.195). The groups' serum AOPP, apelin, and 8-OHdG levels are presented in Table 3. The AOPP level of the focal epilepsy group was higher than that of the control group (Fig. 1). The serum apelin level of the patients with generalized epilepsy was lower than that of the control and complicated febrile groups (Fig. 2) It was determined that the patients in the generalized epilepsy group had had more seizures (Fig. 3).

### *Correlations*

The correlations between the parameters of all participants were analyzed with the Spearman's correlation test. The significant correlations are presented in Table 4 (see Fig 4).

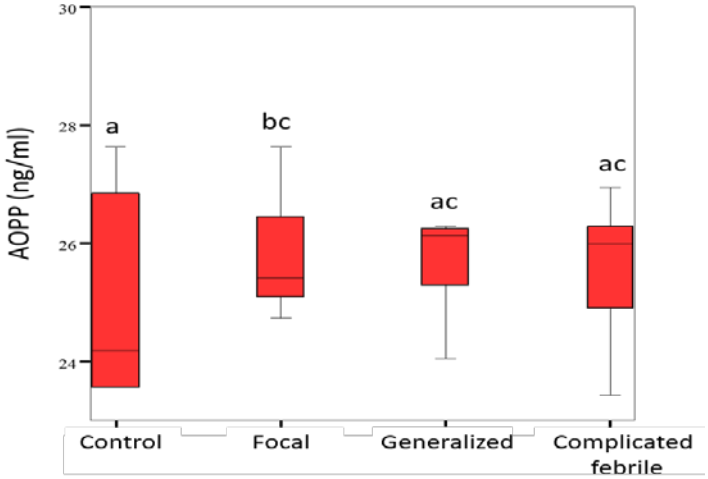


**Figure 1.** Comparison of serum AOPP level of the patient groups and the control group. Different letters indicate a significant difference at alpha level of $p \leq 0.05$.

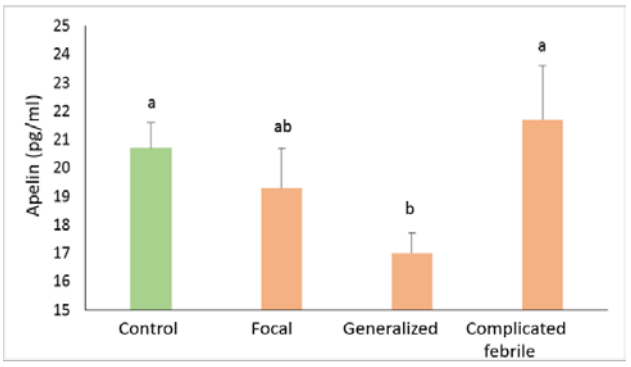


**Figure 2**. Comparison of serum Apelin level of the patient groups and the control group. Different letters indicate a significant difference at alpha level of $p \leq 0.05$.

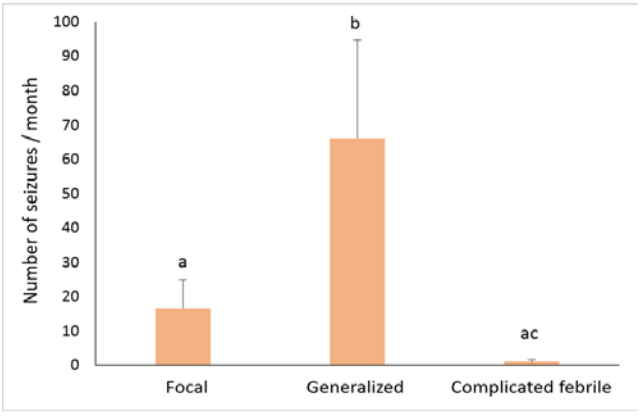


**Figure 3.** Comparison of number of seizures/ month of the patient groups. Different letters indicate a significant difference at alpha level of $p \leq 0.05$.

**Table 3.** Comparison of the mean BMI, serum 8-OHdG, apelin, AOPP levels and number of seizure/ month according to control and patient groups.

| | Control (n=10) | Focal (n=13) | Generalised (n=7) | Complicated Febril (n=6) | p |
|---|---|---|---|---|---|
| | | | Median± Std Deviation | | |
| **BMI (kg/m²)** | 17.71±3.40 | 16.62±3.01 | 15.84±3.61 | 14.02±3.31 | 0.195 |
| **AOPP (ng/ml)** | 24.81$^{a}$±1.70 | 25.90$^{bc}$±1.10 | 26.02$^{ac}$±1.55 | 25.51$^{ac}$±1.21 | **0.05** |
| | | | Mean± Std Error | | |
| **Apelin (pg/ml)** | 20.73 $^{a}$±0.92 | 19.34 $^{ab}$±1.46 | 17.03$^{b}$±0.72 | 21.71$^{a}$±1.92 | **0.03** |
| **8-OHdG (pg/ml)** | 42.40±3.62 | 42.72±3.64 | 45.04±6.32 | 44.91±3.20 | 0.96 |
| **Number of seizure/ month** | 0 | 16.51$^{a}$±8.40 | 66.12$^{b}$±28.71 | 1.03$^{ac}$±0.62 | **0.05** |

*8-OHdG; 8-hydroxy-2' -deoxyguanosine, AOPP; Advanced oxidation protein products.*
*BMI; Body mass index*
*Different letters indicate a significant difference at alpha level of p≤ 0,05.*

**Table 4.** Relationships of some parameters to each other

| Parameters | | Apelin (pg/ml) | AOPP (ng/ml) | BMI (kg/m²) | Number of seizure/ month |
|---|---|---|---|---|---|
| **8-OHdG (pg/ml)** | *rho* | **-0.266** | -0.105 | -0.031 | 0.066 |
| | *p* | **0.048** | 0.439 | 0.824 | 0.740 |
| **Age)** | *rho* | 0.084 | -0.263 | **0.399** | 0.039 |
| | *p* | 0.540 | 0.048 | **0.003** | 0.845 |
| **BMI (kg/m²)** | *rho* | 0.029 | **-0.372** | | **-0.501** |
| | *p* | 0.835 | **0.006** | --- | **0.018** |
| **Number of seizure/ month** | *rho* | **-0.260** | **0.264** | | --- |
| | *p* | **0.050** | **0.050** | | |

*8-OHdG; 8-hydroxy-2' -deoxyguanosine, AOPP; Advanced oxidation protein products.*
*BMI; Body mass index.*

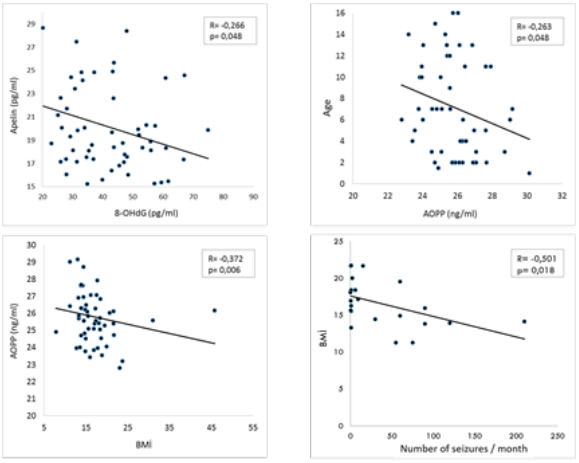


**Figure 4.** Relationships graphs of some parameters to each other

## Discussion

According to the results of this study, it was determined that the number of epileptic seizures decreased as apelin increased and increased as AOPP increased. It was determined that apelin was especially low in patients with generalized type epilepsy, while it was high in complicated febrile patients with the risk of epilepsy. It was also determined that the number of seizures was higher among the patients with generalized type epilepsy. It was found that the level of 8-OHdG (a DNA damage indicator) decreased as the apelin level increased. The AOPP level was higher in the patients with focal type epilepsy than in the control group and was shown to decrease as age and BMI increased. The obtained results were discussed under the following headings by comparing them with the literature.

***Apelin can decrease the number of seizures by preventing oxidative DNA damage***

A difference was observed between the apelin and 8-OHdG levels in the general comparison between the control and epilepsy groups in this study. When classified based on epilepsy type, it was found that the patients with generalized type epilepsy experienced a more significant decrease in apelin levels than those in the control group. It was also found that there was a negative correlation between apelin and 8-OHdG levels, and a negative correlation between apelin and the number of seizures. After reviewing the relevant literature, it appears that the present study is the first to reveal that apelin might be effective in decreasing the number of epileptic seizures. The studies in the literature reported that apelin is effective in anti-neurodegenerative diseases (10). In the study by Elhady et al. (2018), it was stated that apelin levels did not differ in patients with epilepsy (11). The relevant literature supports the findings of the current study, but does

not make a classification based on epilepsy types. It was found in this study that the apelin level was low in patients with generalized type epilepsy. In a study conducted on rats, it was determined that the epileptic seizure threshold decreased and tonic-clonic lantency was significantly inhibited as a result of apelin13 application, and that apelin13 had a protective role on the cortical neurons (10). Accordingly, the finding that apelin was low and the number of seizures was high in the patients with generalized type epilepsy indicated that apelin had a neuroprotective role. Since the relevant literature was quite limited, more detailed studies are needed for better understanding of the mechanism. In the study by Meral et al. (2011), the apelin level increased among the patients who received antiepileptic drug (valproic acid) therapy (12). This study supports the ideas found in the present study that apelin is a protective neuropeptide against epilepsy and epileptic seizures. Zhang et al. (2011) conducted a study on rats with epilepsy and found that the apelin level increased after an epileptic seizure; thus, this had a protective effect on preventing neuron losses (4).

An important indicator of DNA damage induced by oxidative stress is the measurement of the 8-OHdG level, which indicates nuclear DNA damage (13). A significant difference in 8-OHdG levels was found between the control and epilepsy groups in this study. There are a limited number of studies in the literature. Similar to the results of this study, Jarrett et al. (2008) found that mitochondrial DNA damage appeared during epileptic seizures in experimental animals, but there were no differences in the nuclear DNA damage (14). When the correlation analysis of all the data was made in the present study, a negative correlation was found between apelin and 8-OHdG levels. There is no study which examined the correlation between apelin and 8-OHdG level in the literature. However, an increase in 8-OHdG level induced by the use of some antiepileptic drugs was reported (15). Since the present study included patients who were diagnosed with epilepsy for the first time and had yet to be started on drug therapy, apelin can be thought to prevent DNA damage based on its level. More detailed studies should be carried out to better understand the mechanism.

***AOPP may lead to an increase in the number of seizures***

According to the data obtained in our study, the number of seizures increased as AOPP which was the product of advanced level protein oxidation increased. Additionally, it was found that AOPP levels were higher in patients with focal type epilepsy. The studies in the literature reported that oxidative stress had a role on the occurrence of some neurodegenerative diseases (16, 17). In a study conducted with patients who had epileptic encephalopathy and used an antiepileptic drug, an increase in AOPP levels (compared to the control group) was reported (18). No difference was observed between the control and epilepsy groups in terms of AOPP levels in the present study. it was observed while the AOPP levels in the control group were lower than those of both the focal and generalized type epilepsy. There was a significant increase in AOPP in the focal type epilepsy group (n=13) as compared to the control group, while there was an insignificant difference in the generalized type (n=7). These differences might be due to the low number of patients in the generalized group. Therefore, the data obtained indicated that there was increased advanced level protein oxidation among the patients with focal type epilepsy, regardless of any drug use. Further, the present study found a significant positive correlation between AOPP levels and the number of seizures per month. In a relevant study, no significant correlation was found between the number of seizures per month and AOPP levels in adult patients who had epilepsy, drug resistance, and who used one/three different drugs (19). No significant difference was found in the AOPP levels when compared to the control group in the relevant literature. Different results found in the current study might be due to the fact that the groups consisted of child patients and there was no use of drugs. In fact, another result of this study— the decrease in AOPP level based on the increase in age and BMI— supports this correlation. It was also found in this study that BMI and the number of seizures proportionally decreased. According to these results, it makes sense to observe a decrease in the monthly number of seizures based on the decrease in AOPP level as age increased.

## Conclusions

**1.** It was determined that the number of epileptic seizures decreased as apelin increased and increased as AOPP increased.

**2.** It was determined that apelin was especially low in patients with generalized type epilepsy, but it was high in complicated febrile patients with the risk of epilepsy.

**3.** It was determined that the number of seizures was higher among the patients with generalized type epilepsy.

**4.** It was found that as the level of 8-OHdG—which is a DNA damage indicator—decreased, apelin level increased.

**5.** It was observed that the AOPP level was higher in the patients with focal type epilepsy than in those in the control group.

**6.** It was determined that the AOPP levels decreased as age and BMI increased.

***Ethical Approval:*** *The approval of the Harran University Non-Interventional Clinical Studies Ethics Committee (Date:05/01/2017 Decision No: 17/01/19) was obtained to conduct the study.*

***Author Contributions:***
*Concept: V.A., H.Ç*
*Literature Review: V.A., T.Ö.*
*Design : V.A., H.Ç*
*Data acquisition: V.A., M.Ç.*
*Analysis and interpretation: V.A., T.Ö, M.Ç.*
*Writing manuscript: V.A., T.Ö.*
*Critical revision of manuscript: T.Ö., H.Ç.*

***Conflict of Interest:*** *The authors have no conflicts of interest to declare.*

***Financial Disclosure:*** *This work was supported by the HUBAP (Project # 17051).*

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