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Antiepileptic drug exposure in the juvenile period does not affect cognitive functions and histomorphology of the hippocampus in adult rats

Mehmet Azizoğlu [1], Tevhide Serap Karasalihoğlu [2], Çetin Hakan Karadağ [3], Yasemin Karal [2], Melike Sapmaz Metin [4]

[1] Department of General Pediatrics, Trakya University School of Medicine, Edirne, Turkey
[2] Department of Pediatric Neurology, Trakya University School of Medicine, Edirne, Turkey
[3] Department of Pharmacology, Trakya University School of Medicine, Edirne, Turkey
[4] Department of Histology and Embryology, Trakya University School of Medicine, Edirne, Turkey

ORCID of the author(s)

MA: https://orcid.org/0000-0002-9982-8005
TSK: https://orcid.org/0000-0001-5579-3528
ÇHK: https://orcid.org/0000-0002-4763-986X
YK: https://orcid.org/0000-0003-0096-6676
MSM: https://orcid.org/0000-0001-9623-4116

Corresponding Author
Mehmet Azizoğlu
Kocaeli City Hospital, Dept. of Pediatric Hematology and Oncology
Izmit-Kocaeli-Turkey 41380
E-mail: drazizoglu@hotmail.com

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Abstract

Background/Aim: The impact of long-term antiepileptic drug use during childhood, particularly during critical growth and development phases, remains poorly understood, particularly in terms of its potential side effects on cognitive and locomotor functions in adulthood. This concern is further heightened for patients with a history of multiple drug use.

Methods: In our experimental animal study, 80 rats were divided into eight groups according to gender and the drugs used. Levetiracetam, vigabatrin, and sodium valproate were added to the drinking water from the 4th week to the 12th week postnatally (juvenile period). After the 12th week (adult period), all groups were tested in the following order: the Morris Water Maze, the Contextual Fear Conditioning Test, the Rotarod Performance Test, and a histomorphological investigation of the hippocampus.

Results: The Morris Water Maze Test, which evaluates learning, showed no changes after chronic usage of antiepileptic drugs during the initial 5 days of swimming tests. On the sixth day of memory retention tests, no effect was observed. Additionally, no significant impairment was noted in the Contextual Fear Conditioning Test that assesses associative learning. In the Rotarod test, which evaluates motor coordination, these drugs exhibited no effect on locomotor activity. Furthermore, the histomorphological dissection of the hippocampus revealed no signs of apoptosis or toxicity.

Conclusion: Consequently, the chronic use of levetiracetam, vigabatrin, and sodium valproate did not affect learning, memory, and locomotor activity. Histomorphologically, no neurodegenerative effects on the hippocampus were detected.

Keywords: antiepileptic drugs, cognitive functions, rats, hippocampus

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Introduction

Epilepsy is one of the most common neurological problems in childhood [1]. Antiepileptic drugs (AEDs) are the primary treatment for childhood epilepsy, but they carry the risk of central nervous system (CNS) dysfunction and other adverse effects, which families often find significantly concerning [2-4]. The treatment of drug-resistant epilepsy in patients with antiepileptic drugs beyond infancy becomes complex due to the potential long-term consequences of early drug exposure. Such exposure may disrupt brain development, leading to impaired nervous system function, cognitive difficulties, and motor deficits in adulthood. The effects of long-term use of antiepileptic drugs during childhood, particularly during the growth and development period, on cognitive and motor functions in adulthood are not well understood. The use of multiple AEDs can make it complex to identify the side effects related to the drugs, especially over the long term. Therefore, experimental animal studies with homogeneous groups are needed to assess the long-term side effects.

Human studies aimed at defining the long-term side effects of antiepileptic drugs used in childhood are limited due to ethical considerations. As a consequence, more animal-based experimental studies are required. In this regard, various methods can be leveraged to measure the cognitive (e.g., learning and memory) and locomotor (e.g., mobility, swimming speed, unit time) functions of rats. We aimed to investigate the long-term side effects of antiepileptic drugs, used in childhood, on learning, memory, and motor functions in adulthood, by conducting studies with rats.

Materials and methods

This experimental study was conducted following the principles and procedures outlined in the National Institutes for Health Guide for the Care and Use of Laboratory Animals. Moreover, the experimental protocol received approval from the local ethics committee. The study was carried out in the laboratories of the Pharmacology Department, as well as the Histology and Embryology Department.

Animals

In this study, a total of 80 Wistar rats (40 males and 40 females) at 24 days old were used. The offspring rats, weaned from their mothers on the 24th postnatal day, were kept four per cage under controlled conditions. These conditions included a temperature of 22 ± 2°C and a 12:12 light-dark cycle, with lights turned on at 7 a.m. The rats had free access to both food and water.

Experimental design

The rats were divided into eight groups (four groups of males and four groups of females, n=10 for each group). The groups and treatments are outlined in Table 1. Rats were weighed weekly from the 4th to the 12th weeks (adult period) [5]. Levetiracetam (Keppra 100 mg/ml oral solution, UCB Pharma), sodium valproate (Depakin oral solution 200 mg/ml, Sanofi Aventis), and vigabatrin (Sabril 500 mg tablet, Sanofi Aventis) were added to the daily drinking water (Table 1). Daily water consumption and nutritional status were monitored. Dosages were determined based on the maximum therapeutic drug doses used for children and in previous studies [6]. Drug dosing was calculated according to weekly weights, taking into account that the daily water consumption of a rat weighing 100 g is about 10–12 ml [7]. No instances of death or illness were observed during the study period.

Table 1: Groups and treatments

Group	Code	Treatment
Control male	CM	Free water
Control female	CF	
Levetiracetam male	LM	65 mg/kg/day in drinking water
Levetiracetam female	LF	
Sodium valproate male	SVM	50 mg/kg/day in drinking water
Sodium valproate female	SVF	
Vigabatrin male	VM	100 mg/kg/day in drinking water
Vigabatrin female	VF	

Evaluation of cognitive functions and locomotor activity in rats

Morris Water Maze: Since its conceptualization by Richard Morris, this test has been extensively utilized in learning and memory studies on rodents [8,9]. It constitutes a circular pool (1.5 m diameter, 45 cm high), filled with water to a depth of 30 cm. The water's temperature was uniformly maintained at 21±1°C. A square platform measuring 10 × 10 cm was submerged 2 cm below the surface in the water tank. An inert black dye was infused into the water to render the platform invisible to the rat. For the appearance of external cues, the room walls were equipped with fixed spatial cues throughout the experiments. The pool was virtually partitioned into four equivalent quadrants. The escape platform was centrally located in the southwest quadrant. The animal's swimming behavior was observed using software (Ethovisiton XT 11.0, Noldus, The Netherlands) that analyzed the imagery procured from a ceiling-mounted camera overseeing the pool.

In the experiments' initial 5 days (acquisition phase), rats were placed into water from four different starting points. Each day, we randomly used each of these starting points once. We orientated the rats to face the wall of the pool at one of the starting points. If a rat failed to find the hidden platform within 60 s, we assisted the rat in locating it. Each rat was permitted to remain on the platform for 15 s. The intertrial interval (the gap between consecutive tests on the same day) was 8 min. After completing the swim tests, we dried the rats and returned them to their cages.

On the sixth day, we removed the platform from the pool and introduced the rat into the water from a previously unused starting point; it was then allowed to stay in the pool for 60 s (probe test). We then removed it from the pool, dried it, and returned it to its cage.

The parameters we recorded in the acquisition phase included the latency to find the platform, the mean distance to the platform, the duration spent in the pool's 10-cm perimeter (a thigmotaxis parameter), and swim speed. The data obtained on the same day (from four trials) was treated as that day's average (average of results from four trials on the same day). In the probe trial on the sixth day, we recorded parameters including latency to reach the target quadrant, time spent in the target quadrant, duration spent in the 10-cm perimeter of the pool, and swim speed.

The Contextual Fear Conditioning Test: This is a behavioral test used to evaluate fear-based (amygdala-based) memory in rats [10]. The equipment (FCS 21200-R, COMMAT,

Turkey) includes a soundproof outer cage with a test chamber made of transparent Plexiglas that contains a metal grid floor. This floor, comprised of parallel stainless-steel rods, is attached to an electric shock device. The test chamber walls also feature visual cues. The rat's freezing behavior is recorded by a connected computer through a mounted video camera located above the testing chamber. On the test's initial day, the rat is placed inside the test chamber and observed for 7 min. During this time, a foot shock (0.5 mA, 1 s) is administered at the 2nd, 4th, and 6th-minute intervals. Twenty-four hours later, the rat is placed back into the same cage for 5 min and is not subjected to any foot shocks. The freezing behavior of the rat on this second day is then automatically recorded by the software.

Rotarod Test: The rotarod test was utilized to assess the motor coordination of the rats. The apparatus comprised a rotating rod with a non-slippery surface, having a diameter of 3 cm and a length of 40 cm, which was placed at a height of 45 cm. The rod was divided into four equal sections (Rotamex 4/8, Columbus Instruments, USA). Each animal was positioned on the rotating rod, which operated between 4 and 20 rpm, and the duration the animal remained on the rod was recorded. This process was repeated three times for each rat. The motor coordination of the rat was evaluated based on the longest time that the animal managed to stay on the rotating mill [11].

Histomorphological Study: Following the completion of behavioral tests, the animals were anesthetized and decapitated. Their brain tissues were excised and preserved in 10% neutral formaldehyde for 3 days. These tissue samples were then embedded in paraffin blocks, from which sections of 5-µm thickness were obtained. The obtained sections were finally stained with hematoxylin and eosin.

Statistical analysis

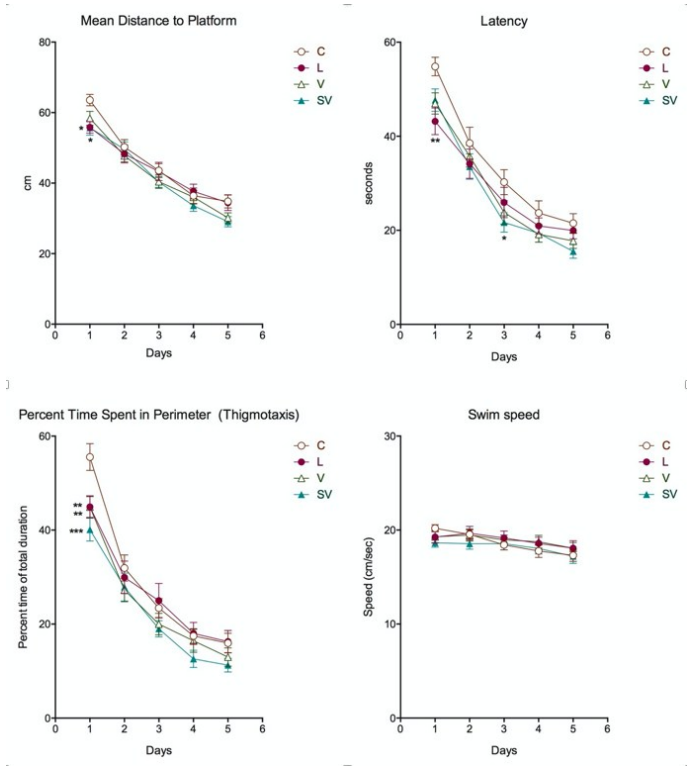
Descriptive statistics were used to evaluate the data. In the analysis of data obtained from Morris Water Maze Test trials, we used a two-way repeated measures analysis of variance (ANOVA) and a *post-hoc* Bonferroni test. A one-way ANOVA and a *post-hoc* Bonferroni test were used to compare data obtained from the probe tests of the Morris Water Maze, the contextual fear memory test, and the Rotarod test. Analyses were performed on GraphPad Prism 6.0 for Mac OSX, Machine ID: 60B52B3D040. A *P*-value of <0.05 was considered significant.

Results

The data derived from the male and female groups were assessed both as separate entities and as combined treatment categories (e.g., merging CM and CF groups into group C, and LM and LF groups into group L).

Data from the Morris Water Maze Test trials: The mean distance to the platform and latency (i.e., the time taken to reach the platform) during swimming were used as learning indicators in the trials carried out over the first 5 days. A two-way repeated measures ANOVA (treatment × day) on the mean distance to the platform showed a non-significant treatment effect (F [3.76]=1.68; P=0.179) and a significant day effect (F [4.304]=180.40; P<0.001). The interaction was not significant (F [12.304]=1.41; P=0.159). These results suggest that the animals learned the platform's location through consecutive learning trials, with no apparent difference in learning performance among the groups (Figure 1). Post-hoc analysis revealed that the performance of the levetiracetam and sodium valproate groups on the first day was significantly better than that of the control group (P<0.05); however, no significant differences were observed in the following days. A two-way repeated measures ANOVA (treatment × day) on latency revealed a significant treatment effect (F [3.76]=3.30; P=0.025) and a significant day effect (F [4.304]=142.90; P<0.001). The interaction was non-significant (F [12.304]=0.91; P=0.537). A post-hoc analysis showed significantly better performances for the levetiracetam group on the first day (P=0.002) and for the sodium valproate group on the third day (P=0.033).

Figure 1: Morris water maze learning trial performances in combined groups. Each data point indicates average of the result obtained from four swimming session in the same day. Vertical bars indicate standard error of mean. Groups: C, control; L, levetiracetam; SV, sodium valproate; V, vigabatrin. Each group contains male and female rats (n=20 for each group). *P<0.05; **P<0.01, ***P<0.001 compared to control group on the same day

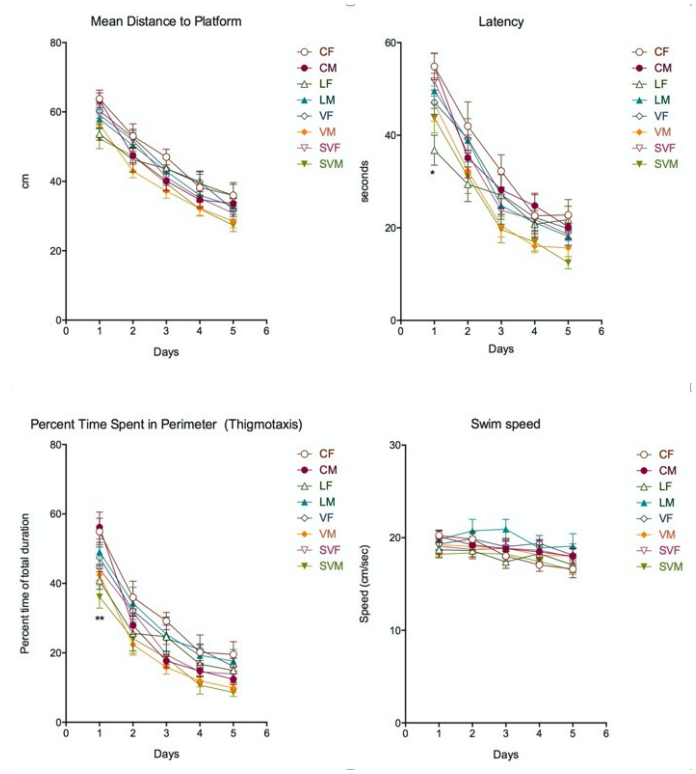


Time spent around the pool's perimeter is an indicator of thigmotaxis, a preference to stay near the pool wall, which is often a sign of an animal's anxiety. A two-way repeated measures ANOVA (treatment × day) performed on thigmotaxis reported a non-significant treatment effect (F [3.76]=2.72; P=0.051) along with a significant day effect (F [4.304]=195.9; P<0.001). The interaction did not yield significant results (F [12.304]=1.74; P=0.058). In the post-hoc analysis, the thigmotaxis level on the first day in the control group was higher than that in levetiracetam (P=0.007), vigabatrin (P=0.007), and sodium valproate groups (P<0.001).

A two-way repeated measures ANOVA (treatment × day) on swim speed yielded a non-significant treatment effect (F [3.76]=0.48; P=0.695) and a significant day effect (F [4.304]=10.69; P<0.001). Although a slight decreasing trend in swim speed on consecutive days was observable, a statistically significant decrease in swim speed compared to the first day was only seen in the control group beginning on the third day (P<0.05 on day 3 and P<0.001 on days 4 and 5 compared to day 1). The interaction was not significant (F [12.304]=0.82; P=0.625).

When treatment groups were analyzed as independent units without merging the male and female groups (Figure 2), a two-way repeated measures ANOVA (treatment × day) on the average distance to the platform unveiled a significant treatment effect (F [7.72]=2.20; *P*=0.045). However, post-hoc evaluations (Bonferroni test) did not highlight any significant disparities between the control group and other treatment groups on the same days. The interaction was not significant (F [28.288]=1.06; *P*=0.394). The animals learned the platform's location through consecutive trials. A two-way repeated measures ANOVA (treatment × day) on latency signified a significant day effect (F [4.288]=144.1; *P*<0.001) and a significant treatment effect (F [7.72]=2.65; *P*=0.017). The interaction was not significant (F [28.288]=1.06; *P*=0.393). Post-hoc evaluations revealed a statistically significant disparity between the control and levetiracetam female groups on the first day (*P*<0.01), and this difference persisted on the second day.

Figure 2: Morris water maze learning trial performances in standalone groups. Each data point indicates average of the result obtained from four swimming session in the same day. Vertical bars indicate standard error of mean. Groups: C, control; L, levetiracetam; SV, sodium valproate; V, vigabatrin; F, female; M, male (n=10 for each group). *P<0.01; **P<0.001 compared to control group on the same day

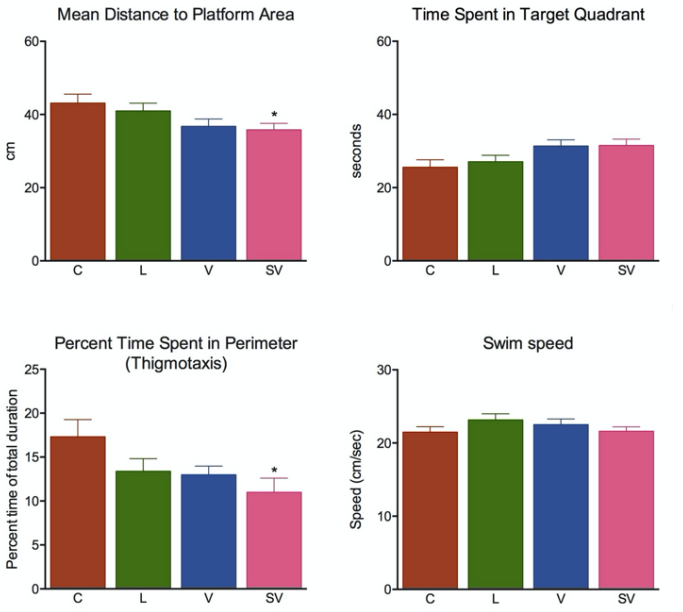


A two-way repeated measures ANOVA (treatment × day) on thigmotaxis revealed a significant treatment effect (F [7.72]=3.13; *P*=0.006) and a significant day effect (F [4.288]=194.40; *P*<0.001). Thigmotaxis gradually decreased on consecutive days. The interaction was not significant (F [28.288]=1.23; *P*=0.202). In post-hoc analysis, the thigmotaxis level on the first day in the male group treated with sodium valproate was statistically significantly lower than that of the control male group (*P*<0.001); this difference disappeared on the second day.

A two-way repeated measures ANOVA (treatment × day) on swim speed revealed a non-significant treatment effect (F [7.72]=0.94; *P*=0.481) and a significant day effect (F [4.288]=10.60; *P*<0.001). There was a slight decreasing trend in swim speed among the female control group on consecutive days (*P*<0.05 on day 3, *P*<0.01 on day 4, and *P*<0.001 on day 5 compared to day 1); the other groups did not show such a statistically significant difference in swim speed. The interaction was not significant (F [28.288]=0.83; *P*=0.721).

Morris Water Maze Test probe data: We used the mean distance to the platform area and time spent in the target quadrant as indicators of memory retention in probe trials performed on the sixth day. An ANOVA on the mean distance to the platform area revealed a statistically significant better performance in the sodium valproate group compared to the control group (*P*<0.05). However, we did not observe such a difference in the time spent in the target quadrant. Treatment groups showed lower thigmotaxis than the control group, however, the difference was statistically significant only in the sodium valproate group (*P*=0.028). There was no statistically significant difference in swim speed values among the treatment groups (Figure 3).

Figure 3: Morris water maze probe trial performances in combined groups. Vertical bars indicate standard error of mean. Groups: C, control; L, levetiracetam; SV, sodium valproate; V, vigabatrin. Each group contains male and female rats (n=20 for each group). *P<0.05 compared to control group



When treatment groups were analyzed independently, without combining the male and female groups (Figure 4), an ANOVA on the mean distance to the platform area revealed a statistically significant better performance in the male control group compared to the female control group (*P*=0.022). However, when the parameter of time spent in the target quadrant was analyzed, no such difference was detected. Thigmotaxis was high in female control animals compared to other groups. Statistically significant differences were observed between the female control group and the male control group (*P*=0.012), as well as the levetiracetam female group (*P*=0.008). Regarding swim speeds, no statistically significant differences were detected among the treatment groups.

Fear Conditioning Test: Irrespective of whether the analyses were performed on combined male and female groups or stand-alone groups, the ANOVA analyses indicated no statistically significant difference among the groups (Figure 5).

Rotarod Test: ANOVA analyses on combined male and female groups, as well as on stand-alone groups, revealed no statistically significant difference in the rotarod performance of animals among groups (Figure 6).

Figure 4: Morris water maze probe trial performances in standalone groups. Vertical bars indicate standard error of mean. Groups: C, control; L, levetiracetam; SV, sodium valproate; V, vigabatrin; F, female; M, male (n=10 for each group). *P<0.05, **P <0.01 compared to control female group

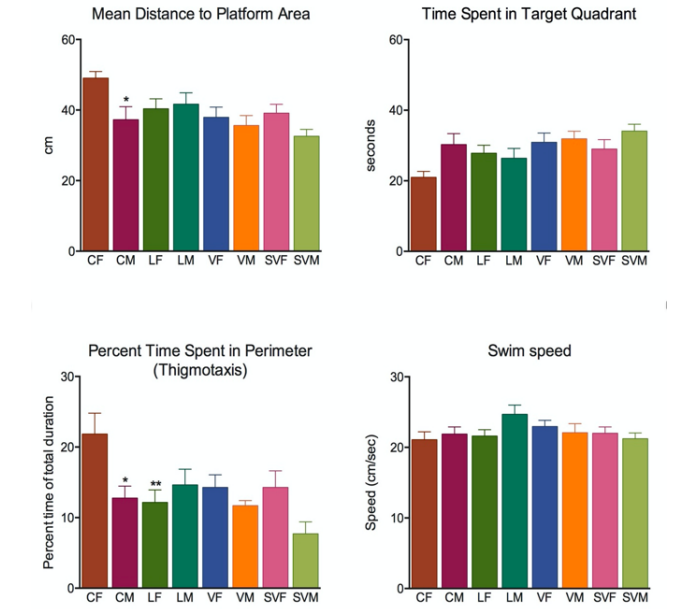


Figure 5: Fear condition test results as combined (left) and standalone groups (right). Vertical bars indicate standard error of mean. Groups: C, control; L, levetiracetam; SV, sodium valproate; V, vigabatrin, F, female; M, male. n=20 for combined groups (10 male and 10 female); n=10 for standalone groups

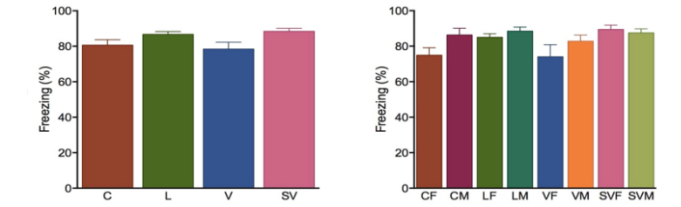
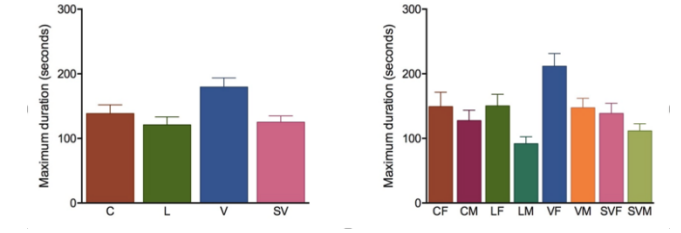


Figure 6: Rota-rod performances as combined (left) and standalone groups (right). Vertical bars indicate standard error of mean. Groups: C, control; L, levetiracetam; SV, sodium valproate; V, vigabatrin, F, female; M, male. n=20 for combined groups (10 male and 10 female); n=10 for standalone groups



Histology: Evaluations of Hematoxylin and Eosin-stained coronal sections were conducted using different magnifications in a light microscope. Regarding general appearance and cellular organization, no morphological differences were observed among the control, drug, female, and male groups in the hippocampus CA1, CA2, CA3, and the dentate gyrus regions (Figure 7, Figure 8).

Upon high magnification examination (400×) of the CA1 regions, neurons close to each other in the male and female control groups were found to exhibit normal cellular morphology. Long-term exposure to drugs such as levetiracetam, sodium valproate, and vigabatrin has been linked to histopathological findings suggestive of cell toxicity or death, not only in neurons but also in other cell types. Symptoms include pronounced eosinophilia, mononuclear cell infiltration, presence of eosinophilic granules, extensive macrophage aggregation, edema, cell membrane degradation, and undetermined nuclear degradation or condensation (Figures 9 and 10).

Figure 7: a-d. Hippocampus microphotographs of Female control (a), Levetiracetam (b), Sodium valproate (c) and Vigabatrin (d) group H+E, 100x

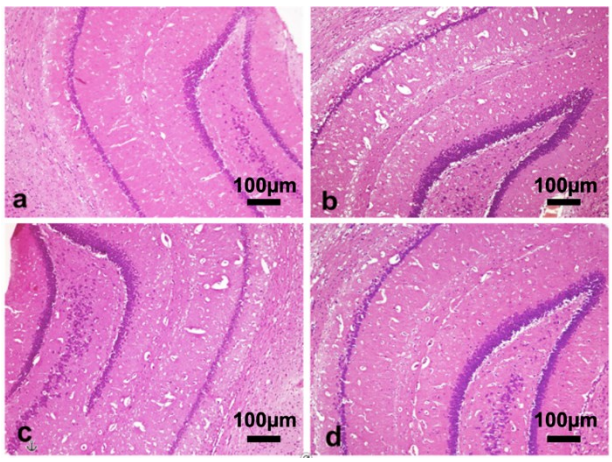


Figure 8: a-d. Hippocampus microphotographs of Male control (a), Levetiracetam (b), Sodium valproate (c) and Vigabatrin (d) group H+E, 100x

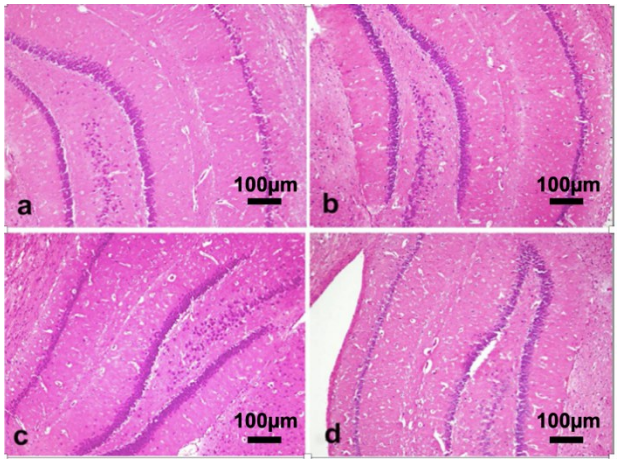


Figure 9: a-d. Histomorphological changes were not detected in the CA1 region female control (a), Levetiracetam (b), Sodium valproate (c) and Vigabatrin (d) group H+E, 400x

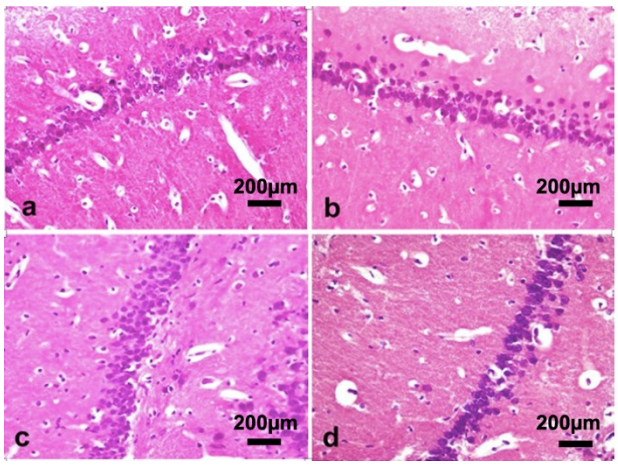
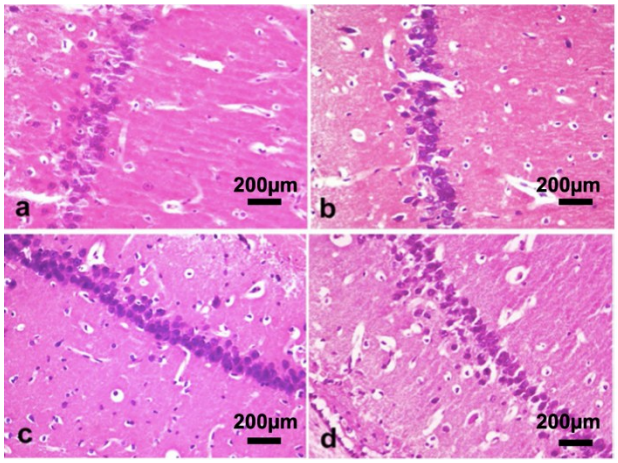


Figure 10: a-d. Histomorphological changes were not detected in the CA1 region male control (a), Levetiracetam (b), Sodium valproate (c) and Vigabatrin (d) group H+E, 400x



Discussion

The impact of epilepsy on cognitive functions in children, whether resulting from the disease itself or the side effects of long-term antiepileptic medications, is not fully understood. Antiepileptic drugs may contribute to memory impairment, decreased vigilance, and psychomotor slowing. Current literature typically examines the effects of levetiracetam (LEV) on adult patient groups' cognitive function [12]. Levetiracetam, a newer drug, is believed to have a neuroprotective effect due to its anti-inflammatory and anti-apoptotic characteristics [13]. Side effects such as motor coordination disorders, ataxia, agitation, behavioral alterations, hyperactivity, irritability, and fatigue have been reported when levetiracetam is used [14]. However, recent studies support the safe administration of levetiracetam, even in extremely preterm infants [15]. Experimental studies have evaluated short-term drug applications, alongside cognitive and locomotor activities [16]. The Morris Water Maze, a test commonly used to identify learning and memory issues related to the hippocampus in rodents suffering from brain disorders, was used in this study [17,18]. Naive rats, administered with LEV at 65 mg/kg/day from the 4th to 12th weeks (adult period), demonstrated no difference in learning performance among groups. Our findings suggest that LEV does not impact spatial memory in rats, as they showed improved performance over successive test days, marked decreased time to find the platform and shorter travel distances. Furthermore, LEV administration from day 4 to 14 did not hinder the learning process. We concluded that long-term use of levetiracetam does not affect the memory and learning skills of rats, as evidenced by the Morris Water Maze Test in our study.

The mean distance to the platform and latency (time to reach the platform) parameters reached during swimming were utilized as indicators of learning in trials conducted during the initial five days. A non-significant treatment effect was revealed on the mean distance to the platform. Lamberty et al. [19] discovered that LEV did not obstruct learning in rats when tested in the Morris Water Maze, except for a high dose of sodium valproate (VPA) (300 mg/kg). However, rats given this high dose of VPA swam faster, possibly negatively affecting their maze performance due to increased activity levels. Interestingly, we noted a sudden drop in swimming distance on our experiment's first day. This decrease was not due to less time given to the animals but instead points towards a potential issue with the animals' movement, not a positive outcome. This problem disappeared in the subsequent days. Interpreting these results poses a challenge due to our testing method's limitations. Animals may exert varying levels of effort for the reward, and some might struggle to locate the platform. The experiment's stress could cause some animals to freeze, impeding their learning process. However, we did not observe this behavior in our study.

Previous research has shown that levetiracetam can enhance cognitive abilities such as visual and working memory, motor skills, reaction time, focus, and overall intelligence [20]. However, our study did not find any significant improvement or decline in cognitive function with levetiracetam alone. Conversely, another study reported that levetiracetam did not impact the spatial recall ability of normal mice [21]. A different study reported cognitive issues in mice post-administration of high doses of levetiracetam (310 mg/kg p.o.) for 45 days. This negative effect was attributed to increased oxidative stress. The researchers emphasized the need for patients' close monitoring, particularly for those receiving long-term levetiracetam treatment [22]. The question of whether levetiracetam can enhance memory in individuals without epilepsy remains unanswered. Additional animal and human clinical trials, employing various cognitive tests, are needed to determine levetiracetam's impact as a supplemental treatment on cognitive function in non-epileptic individuals. Our current research established that levetiracetam alone did not noticeably affect cognition in our experimental model.

Repeated doses of levetiracetam did not significantly impair short-term memory, spatial awareness, or emotional recall in rats. However, a single, large dose of the drug resulted in difficulties with long-term memory, movement, and emotional memory. Importantly, problems with emotional memory were temporary and vanished with repeated dosing [12]. Since our study involved rats without epilepsy, it is challenging to directly apply these findings to humans with epilepsy. Further research is necessary to fully comprehend the safety of levetiracetam, particularly in animals with epilepsy.

These results corroborate previous research demonstrating VPA's adverse impact on learning and memory in rats [23]. Notably, these studies have shown that VPA can impair spatial learning and memory at doses that are comparable to, or even lower than those effective in preventing seizures in various rat epilepsy models [13,16]. In our study, VPA was administered at a dose of 50 mg/kg/day, yet it was not effective in improving the learning and memory of normal rats.

Edalatmanesh et al. [6] discovered that VPA markedly improved cognitive impairments and reduced lipid peroxidation in TMT-treated rats. VPA was identified to have anxiolytic activity both in a standard elevated plus-maze and in conflict tests in the rat [24,25]. However, detecting distinct behavioral changes induced by levetiracetam in healthy rodents can be challenging. This might clarify why levetiracetam effectively reduces anxiety in a specialized, conditioned version of the Vogel test, but not in the standard test. Recent literature has not presented the effect of vigabatrin on learning and cognitive function in naive rats. In our study, vigabatrin did not affect learning and cognitive function. This could explain the absent effects of levetiracetam in normal animals on the elevated plus-maze, perhaps due to the relatively low-stress levels associated with this test.

Long-term exposure to drugs such as levetiracetam, sodium valproate, and vigabatrin has been associated with histopathological findings indicative of potential cell toxicity or neuronal death. Preece et al. [26] reported that vigabatrin (VGB) led to cerebellar and cortical white-matter lesions. In a different study, phenytoin, levetiracetam, carbamazepine, and valproic acid were found to potentially accelerate axonal healing [27]. Our study did not identify any histopathological deterioration in rat brain tissue from exposure to levetiracetam, sodium valproate, or vigabatrin. The Fear Conditioning test, a measure of fear-based memory, yielded no different effects compared to the

control group. No studies mentioned in the existing literature examine the side effects of these antiepileptic drugs.

In our study, we found that the long-term use of levetiracetam, vigabatrin, and sodium valproate in young rats had no impact on cognitive functions in adulthood. No changes were detected in the hippocampal tissues during histomorphological examination. According to our knowledge, there is no study investigating the long-term effects of these drugs administered in young animals on the cognitive function of rats. Our results suggest the safety of long-term use of levetiracetam, vigabatrin, and sodium valproate regarding cognitive functions. However, one must be cautious when extrapolating these findings to humans. Observational studies investigating the effects of long-term use of these drugs on cognitive function should be designed and conducted. The influence of the disease itself on cognitive function should also be examined. For this purpose, by using appropriate animal epilepsy models, the effects of the disease on the cognitive functions of the animals can be assessed.

Limitations

While we ensured homogeneity in our rat groups for this study, the number of rats could have been higher. Our limitation was that the experimenter had to handle all the rats individually, as varied handling by different people might induce behavioral differences in the rats. We also considered drug administration via oral gavage, but we were constrained by the large rat population and the potential for increased anxiety this method might cause. The complete application of such studies to clinical practices would benefit from multicenter human trials.

Conclusion

Antiepileptic drugs may affect cognitive and locomotor functions, especially in the long term. In light of our results, levetiracetam, vigabatrin, and sodium valproate given during young period of rats had no effect on cognitive functions and on hippocampal tissues. According to our results, it can be speculated that these drugs are safe with respect to cognitive functions. Our findings need confirmation by observational studies in humans.

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From hashtags to healing: Social media insights on kinesio taping in Türkiye

Mustafa Hüseyin Temel [1], Fatih Bağcıer [2]

[1] Sultan 2 Abdulhamid Han Training and Research Hospital, Physical Medicine and Rehabilitation Clinic, Istanbul, Türkiye
[2] Basaksehir Cam Sakura City Hospital, Physical Medicine and Rehabilitation Clinic, Istanbul, Türkiye

ORCID of the author(s)

MHT: https://orcid.org/0000-0003-0256-5833
FB: https://orcid.org/0000-0002-6103-7873

Corresponding Author
Mustafa Hüseyin Temel
Barbaros, Veysi Paşa Sk. No:14, 34662 Üsküdar, İstanbul, Türkiye
E-mail: mhuseyintemel@gmail.com

Ethics Committee Approval
Considering the absence of an *in vivo* application, the study did not necessitate an ethics committee application, aligning with prior scholarly evidence. Since no patient data were collected, the study did not need to be submitted to a clinical research ethics committee and was exempt from the requirement for informed consent.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Social media provides valuable insights into healthcare practices, including kinesio taping (KT), a technique used for pain relief and stability. Despite its popularity, there is limited research on KT content on social media. This study aims to analyze social media posts related to KT in Türkiye.
Methods: The study was conducted by analyzing posts on social media platforms including Twitter, Instagram, Facebook, and YouTube. The hashtags '#kinezyobant', '#kinezyobantlama', and '#kinezyoteyp', as well as the keywords 'kinezyobant', 'kinezyobantlama', and 'kinezyoteyp' were used as search criteria. The collected data were categorized into different groups: healthcare organizations, commercial entities, physicians, news sources, users, and non-physician healthcare professionals.
Results: A total of 445 posts related to KT were identified across various social media platforms. YouTube boasted the highest number of posts, followed by Twitter, Facebook, and Instagram. Non-physician healthcare professionals contributed the most posts, whereas physicians and news sources posted relatively less. Twitter saw the highest number of user-generated posts, while Instagram displayed a higher prevalence of posts for commercial purposes. Among all platforms, Facebook accounted for the highest number of posts by healthcare organizations.
Conclusion: Social media platforms, especially YouTube, are crucial in disseminating information about KT. Non-physician healthcare professionals notably contribute to the online discourse, potentially highlighting the need for enhanced KT education among physicians. Facebook offers benefits for patients to communicate with and engage in healthcare organizations. However, addressing concerns about misinformation and privacy, along with promoting responsible usage of these platforms in healthcare, is crucial.

Keywords: kinesio taping, social media, healthcare

Introduction

Social media has revolutionized the way people communicate and interact in the digital era. It encompasses a variety of online platforms and applications that allow users to create, share, and discuss content, ideas, and information. Social media platforms such as Facebook, Twitter, Instagram, and YouTube have become essential parts of people's lives, shaping personal relationships, business networking, and even political movements [1].

Social media is vital for treatment options and health information, serving as a platform where healthcare organizations, professionals, and patients can exchange valuable insights and resources. It enables users to access a wealth of health-related information, enhancing health literacy and empowering individuals to make informed decisions. Real-time communication on social media bridges geographical barriers, facilitating direct interaction between patients and healthcare providers and improving accessibility to expert advice. Additionally, it fosters peer support by connecting individuals with similar health challenges [2].

Analyzing social media for treatment methods is crucial as it provides valuable real-world data and insights into healthcare practices. User-generated content on social media platforms, such as discussions, testimonials, and experiences, offers a wealth of information about treatment effectiveness, side effects, and patient perspectives [3]. These analyses enable healthcare professionals and researchers to better understand treatment outcomes, identify emerging trends, and recognize patient preferences and potential adverse reactions.

Kinesio taping (KT) is a therapeutic technique that involves applying a specialized elastic tape to the body. This technique aims to provide support, stability, and pain relief. The tape is designed to mimic the properties of human skin, which allows for unrestricted movement while gently giving mechanical assistance to the targeted area [4]. KT is frequently used in sports medicine, physical therapy, and rehabilitation settings to help in managing musculoskeletal conditions and injuries. The technique's popularity can be attributed to its non-invasive nature and the potential benefits it offers for pain management and functional rehabilitation [5].

While there is a plethora of research available on social media treatments [6-8], there is a striking lack of studies specifically targeting KT. This has resulted in a noticeable knowledge gap. Therefore, the purpose of this study is to examine the content posted on social media platforms related to KT. In doing so, this research hopes to fill the void in the current literature and offer valuable insights and data on the topic.

Materials and methods

The research was conducted on August 21, 2022, at the Physical Medicine and Rehabilitation Clinic of Üsküdar State Hospital. Given the absence of *in vivo* application, the study did not require an application to an ethics committee, in line with previous scholarly evidence [9].

To ensure the integrity of the social media research, specific measures were undertaken. Before beginning the investigation, the browser's history and cookies were cleared to remove any potential bias or influence from previous online activities. In addition, new accounts were established on the targeted social media platforms to avoid undue interference with the resulting data. On Twitter, the hashtags '#kinezyobant', '#kinezyobantlama', and '#kinezyoteyp' were used as search parameters. Similarly, on Facebook, content related to KT was sought using the keyword "kinezyo bantlama". On Instagram, the hashtags #kinezyobant, #kinezyobantlama, and #kinezyoteyp were employed for content search. Lastly, YouTube was explored using the keywords "kinezyobant", "kinezyobantlama", and "kinezyoteyp".

Groups on Facebook that required membership and their related content were excluded from the study. Additionally, videos containing only text or sound, and videos with loading issues were also not included in the analysis. Similar criteria were followed on Instagram and YouTube, where hidden accounts, posts with only text or sound, and posts with connection-loading problems were excluded. Furthermore, the collected Facebook data, categorized into videos, posts, pages, and groups, were analyzed separately. These categories were then combined with the results from other social media platforms, enabling the categorization of posts, groups, and videos according to the content shared by respective accounts. Notably, categories included healthcare organizations like physical therapy centers and private hospitals, institutions offering KT courses, individuals or organizations engaged in the sale and supply of KT, non-physician healthcare professionals, users sharing personal experiences and expressing opinions and concerns about KT, news-related posts, and physicians. Each post was meticulously classified and evaluated within these established categories to extract valuable insights from the collected data.

Statistical analysis

The behavior of quantitative variables was analyzed using measures of central tendency and variance, notably the mean. The One-Sample Chi-Square test was used to compare the percentages of a categorical variable with population proportions. A statistical significance level of $P < 0.05$ was selected for all cases. Statistical analyses were performed using IBM SPSS (Statistical Package for the Social Sciences) software, Version 21.0, which is specifically designed by IBM Corp. in Armonk, NY for Windows operating system.

Results

Across the various platforms, 445 posts on KT were identified. Fifty-four posts were identified on Instagram, 89 posts on Facebook, 149 posts on Twitter, and 153 posts on YouTube. A comprehensive summary of the overall count of posts across diverse categories on social media platforms is presented in Figure 1.

The analysis of posts related to KT across various users revealed the following distribution: 17 posts from news sources, 24 posts from physicians, 58 posts from general users, 64 posts for promotional purposes, 113 posts from healthcare organizations, and 169 posts from non-physician healthcare professionals. Figure 2 depicts the distribution of posts across these categories on social media platforms.

Table 1: Comparison of the number of posts across different categories on social media platforms.

	Commercial	Physician	News	Non-Physician Healthcare Professional	User	Healthcare Organization	*P*-value
Twitter	11 (17.2%) ✢	5 (20.8%)	8 (47.1%)	70 (41.4%)	41 (70.7%) †	14 (12.4%) ✢	**<0.001****
Instagram	15 (23.4%) †	7 (29.2%)	0 (0.0%)	10 (5.9%) ✢	1 (1.7%)	21 (18.6%)	
YouTube	18 (28.1%)	3 (12.5%)	9 (52.9%)	71 (42.0%)	16 (27.6%)	36 (31.9%)	
Facebook	20 (31.2%)	9 (37.5%)	0 (0.0%)	18 (10.7%) ✢	0 (0.0%) ✢	42 (37.2%) †	

Stats: n (%), p* Pearson Chi-Squared Test, p** Fisher Exact Test, When an independent (similar) relationship between groups is assumed, cells with significantly high or low figures at a 0.05 level are indicated with † (high) and ✢ (low) symbols.

Figure 1: Overall count of posts across diverse categories on social media platforms.

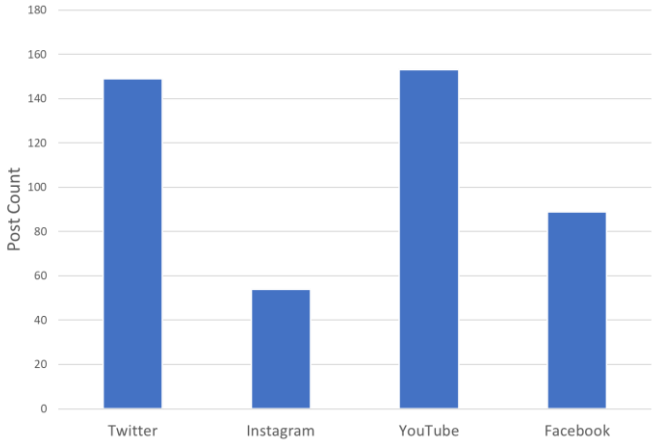
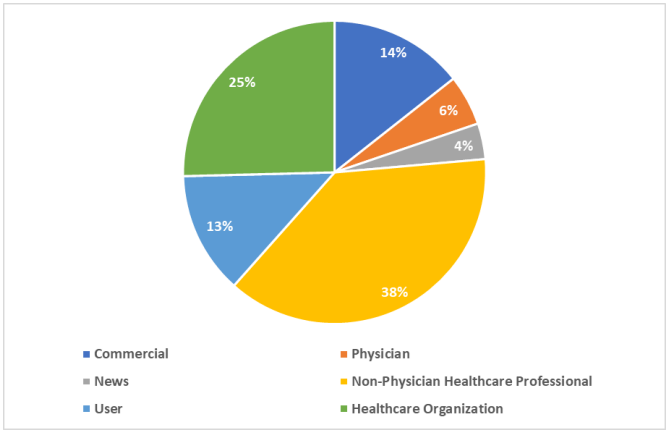


Figure 2: Distribution of posts categorized by the originator of the content.



In comparing the number of posts across various categories on social media platforms, distinct differences were observed. Specifically, Twitter showcased a significantly higher number of user posts, Instagram had a greater frequency of commercial posts, and Facebook displayed a larger volume of posts by healthcare organizations (P<0.001). Table 1 provides a comparison of the number of posts across these categories on different social media platforms.

Discussion

The significance of social media in healthcare and treatment methods is noteworthy. It serves as a potent tool for healthcare practitioners to disseminate valuable information and updates on treatment options, research advancements, and medical technology [10]. Patients can access educational resources, articles, videos, and infographics through social media platforms, simplifying intricate concepts and empowering them to make well-informed decisions about their healthcare [11]. Furthermore, social media nurtures supportive communities where individuals with similar conditions or undergoing specific treatments can connect, exchange experiences, and provide emotional support [12]. It facilitates direct interaction with experts in various modalities, enabling patients and healthcare providers to seek advice and opinions [13]. Additionally, social media allows patients to share real-time feedback and experiences, assisting others in evaluating treatment outcomes [14]. It also serves as a platform for research collaborations, recruitment, and public health campaigns [15]. However, it is crucial to address concerns related to misinformation and privacy while promoting responsible usage and reliance on qualified healthcare professionals [16].

This study aimed to investigate the quantity and distribution of posts related to KT across various social media platforms to provide insights into the online discourse surrounding this treatment modality. To our knowledge, this is the first study that investigates the number and distribution of individuals and organizations posting about KT across different social media platforms in Türkiye.

The social media platform with the highest number of posts identified was YouTube. The prominence of YouTube as a platform for KT-related content can be ascribed to several significant factors. First, YouTube's focus on video content provides an excellent medium for exhibiting KT techniques and offering visual explanations. The interactive feature of videos allows content creators to deliver thorough demonstrations and instructions, making YouTube an ideal platform for disseminating KT-related information [17]. Second, YouTube's wide and diverse user base ensures a vast audience for KT enthusiasts, including healthcare professionals, athletes, and enthusiasts [18]. As a result, this leads to a significant increase in the number of KT-related posts on the platform.

Though physicians play a critical role in diagnosing and managing medical conditions, other professionals such as physical therapists, occupational therapists, and athletic trainers also have specialized expertise in therapeutic interventions [19]. By sharing their knowledge online, these professionals add to the collective understanding and application of KT techniques. The prevalence of posts by non-physician practitioners might suggest the potential limitations of traditional medical education in adequately addressing complementary and alternative therapies. Despite physicians undergoing comprehensive medical training, their curriculum may not extensively cover non-pharmacological interventions or adjunctive therapies. This situation necessitates the involvement of other healthcare professionals who educate patients and fellow practitioners through social media platforms [20].

Twitter has emerged as the platform with the highest number of user posts. This observation aligns with the platform's real-time, fast-paced nature, which encourages users to share their thoughts and updates in concise messages [21]. Twitter serves as a prominent platform for users to communicate and share experiences regarding KT. Users can actively engage in discussions, exchange advice, and disseminate information on this social platform [22].

Instagram shows a higher instance of commercial posts. This is due to the platform's emphasis on visual content and user-friendly features such as shoppable posts and opportunities for influencer marketing, making it an excellent choice for businesses showcasing their products and promotions [23,24]. It seems that fitness influencers, sports therapists, healthcare organizations, physicians, and KT manufacturers have recognized the substantial potential of Instagram's visual content for effectively demonstrating the techniques, efficacy, and versatility of KT.

Facebook has the highest content created by healthcare organizations. By using Facebook as a platform, these organizations can effectively reach and engage with various sectors of the population due to Facebook's diverse user base [25]. This provides healthcare organizations the opportunity to use Facebook to enhance visibility and engage effectively with patients. They can distribute updates, news, and details about their services. Sharing educational materials like articles and videos can help promote health awareness. Direct interactions with patients via comments and inquiries can also foster trust and loyalty [26].

Limitations

The present study has a few limitations that need to be considered. First, the analysis focused specifically on KT posts on social media platforms in Türkiye, which might limit the applicability of the findings to other countries or regions. Moreover, the study examined only the quantity of posts and their distribution in different categories, without evaluating the quality, accuracy, or impact of the information shared on these platforms. To address these limitations, future research could undertake more comprehensive analyses that cover multiple regions, include qualitative assessments of content, and investigate the influence of social media posts on healthcare practices and patient outcomes.

Conclusions

In conclusion, the importance of social media in healthcare is unarguable. It serves as a valuable tool for healthcare professionals, facilitating information sharing, patient connection, and supportive community building. YouTube, in particular, has the highest number of posts, which may be a testament to its effectiveness in demonstrating KT techniques via video. The presence of posts from non-physician practitioners underscores the potential need for comprehensive KT education among physicians. Facebook, on the other hand, offers unique advantages in communication, promotion, and engagement with healthcare organizations regarding KT. However, it is also essential to address concerns over misinformation and privacy issues, while promoting responsible use and collaboration on such platforms.

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A rare primary lung tumor in children: Carcinoid tumor

Özge Ülgen [1], Sinem Can Oksay [1], Yasemin Mocan Cağlar [1], Ayşe Nur Toksöz Yıldırım [2], Saniye Girit [1]

[1] Istanbul Medeniyet University, Department of Pediatric Pulmonology, Istanbul, Turkey
[2] Istanbul Medeniyet University, Department of Pathology, Istanbul, Turkey

ORCID of the author(s)

ÖÜ: https://orcid.org/0000-0002-9271-5446
SCO: https://orcid.org/0000-0001-9801-3181
YMC: https://orcid.org/0000-0002-9609-478X
ANTY: https://orcid.org/0000-0003-1708-0003
SG: https://orcid.org/0000-0001-7556-6568

Corresponding Author
Saniye Girit
Istanbul Medeniyet University, Faculty of Medicine, Department of Pediatrics, Director; Division of Pulmonology, Göztepe Training and Research Hospital, Istanbul, Turkey
E-mail: saniyegirit@gmail.com

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Abstract

Bronchial carcinoids are rare childhood malignancies, comprising only a small proportion of pediatric lung tumors. This report details the case of a 9-year-old girl with persistent pneumonia that lasted one month and remained unresponsive to antibiotic therapy. Radiological imaging revealed atelectasis of the superior lobe of the left lung, while computed tomography showed an endobronchial lesion in the left main bronchus. An endobronchial biopsy confirmed the diagnosis of a typical bronchial carcinoid tumor. The tumor was completely resected using bronchoscopy, and cryotherapy was used to prevent the tumor's recurrence. No evidence of tumor recurrence was observed in subsequent follow-up bronchoscopy. This case underscores the importance of considering bronchial carcinoid tumors in the differential diagnosis of pediatric patients with recurrent pneumonia or wheezing that is resistant to standard treatments. Through early identification and minimally invasive management, such as bronchoscopy and cryotherapy, it is possible to achieve successful outcomes and avoid more extensive surgery. Our findings add to the scarce literature on pediatric bronchial carcinoid tumors and highlight the instrumental role of prompt and accurate diagnosis in improving prognosis.

Keywords: bronchial carcinoid, childhood, bronchoscopy, biopsy, cryotherapy

Introduction

Bronchial carcinoids account for fewer than 0.1% of pediatric malignancies, rendering them extraordinarily rare. Despite representing 42-63% of primary lung malignancies in children, their prevalence significantly declines to 1-2% among adults [1].

Bronchial carcinoids are divided into two subgroups according to their likelihood of malignancy. Typical carcinoids, which are more commonly seen within the pediatric population, tend to have lower malignant potential [2].

In children, bronchial carcinoids are often located endobronchially, leading to airway obstruction, which can mimic benign respiratory conditions. This overlap in clinical presentation often results in misdiagnosis and a delay in achieving an accurate diagnosis and initiating proper treatment. Differential diagnoses to consider include asthma, recurrent pneumonia, bronchial adenoma, foreign body aspiration, and congenital airway malformations such as bronchogenic cysts. Due to the nonspecific presentation of symptoms like wheezing, cough, or recurrent infections, these tumors frequently are misdiagnosed, which leads to delays in timely and appropriate treatment. Diagnostic evaluation, including imaging and histopathological examination, is essential to differentiate bronchial carcinoids from these more prevalent respiratory disorders [3].

In our case presentation, we aimed to discuss a typical bronchial carcinoid tumor case that presented as pneumonia unresponsive to treatment, guided by current literature.

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Case presentation

A 9-year-old girl was admitted with a 1-month history of pneumonia that was unresponsive to treatment and progressive dyspnea. She had been intermittently using inhaled steroids for dyspnea throughout the past year. Her vital signs, as well as her growth and development, showed no abnormalities. She had reduced breath sounds in her left lung compared to the right, and no other abnormalities were observed during the systemic examination. The complete blood count and acute phase reactants, along with other laboratory analyses, were all normal.

The chest X-ray revealed reduced aeration, especially in the superior lobe of the left lung (Figure 1). The contrast-enhanced thoracic CT showed a soft tissue lesion occupying the lumen of the left main bronchus approximately 2 cm distal to the carina (Figure 2). We also observed a complete collapse of the left superior lobe with compensatory expansion of the left inferior lobe. Flexible bronchoscopy revealed a soft tissue mass with mild vascularity on the mucosal surface, causing obstruction approximately 1-2 cm distal to the left main bronchus bifurcation (Figure 3). A punch biopsy was performed on the mass. The histopathological examination revealed a tumorous formation featuring small round nuclei, scant cytoplasm, and a solid-trabecular pattern (Figure 4). This formation tested positive for CD56 (Figure 5) and diffusely for synaptophysin (Figure 6). It had a Ki67 proliferation index of 5% (Figure 7), consistent with a typical carcinoid tumor diagnosis. The Ga-68 DOTA-TATE positron emission tomography-computed tomography (PET/CT) scan found no meta-stability irregularities. The mass was completely excised by bronchoscopy using electrocautery snare and cryoprobe. The patient's symptoms fully resolved after the procedure, and both follow-up bronchoscopies performed in the 2nd and 4th postoperative months showed normal findings with no traces of the lesion. During the 6-month and 1-year post-treatment assessments, the patient was asymptomatic and both the physical examination and imaging results were unremarkable. All of the patient's initial symptoms had subsided and not returned.

Figure 1: X-ray: Decreased aeration particularly in the upper zones of the left lung

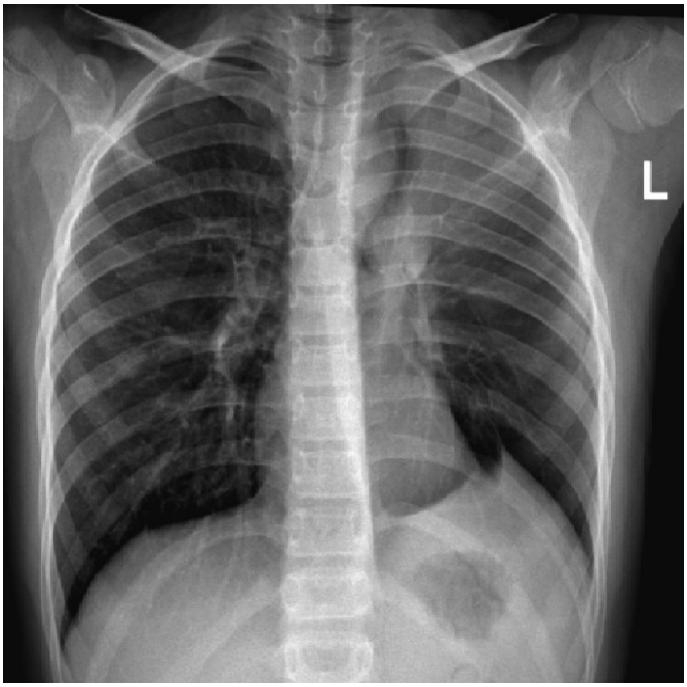


Figure 2: CT: Soft tissue density filling the lumen in the left main bronchus approximately 2 cm distal to the carina (Thick black arrow)

Figure 3: Soft tissue mass with mild vascularity on the mucosal surface, obstructing the lumen

Figure 4: Tumoral formation with small round nuclei, scant cytoplasm, forming a solid-trabecular pattern (Hematoxylin&eosin x40)

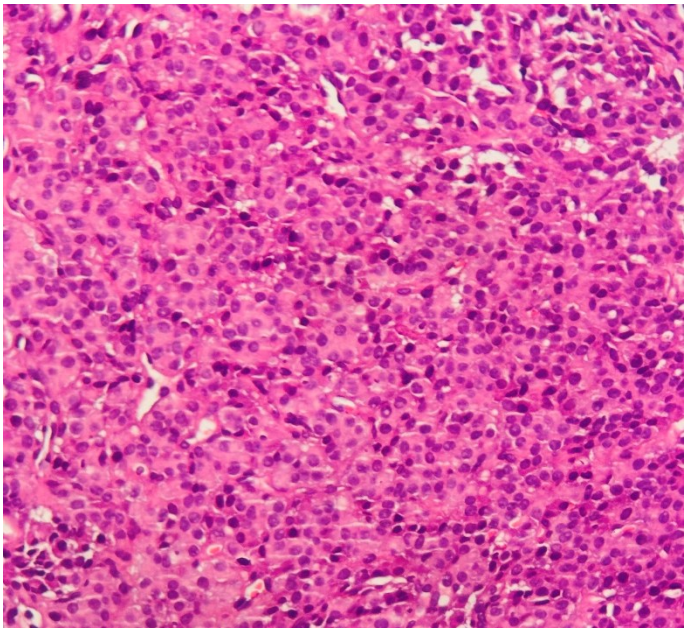


Figure 5: Synaptophysin is diffusely positive in tumor cells (Immunohistochemical analysis X20)

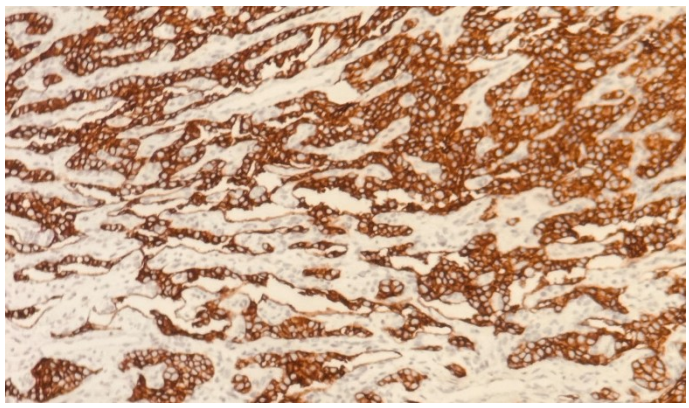


Figure 6: CD56 is diffusely positive in tumor cells (Immunohistochemical analysis X20)

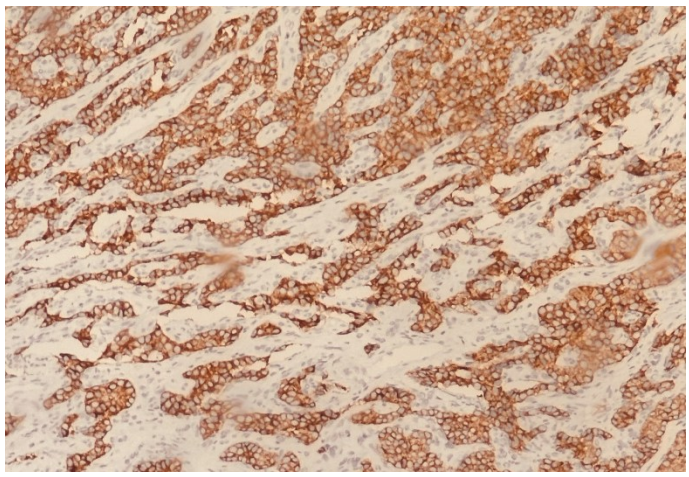
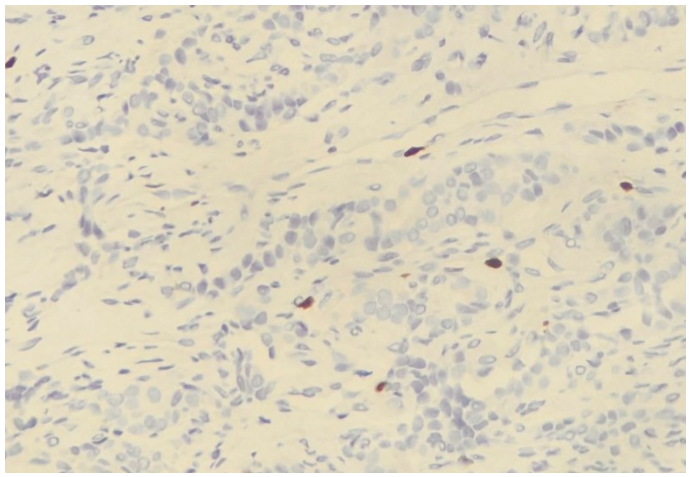


Figure 7: Ki-67 proliferation index is 5% (Immunohistochemical analysis X40)



Discussion

Bronchial carcinoid tumors are well-differentiated malignant neoplasms that originate from Kulchitzky cells, located in the basal layer of the bronchial tissue. These tumors represent 70-80% of all primary malignant lung tumors in children. Typically, carcinoid tumors are centrally located, while atypical carcinoids are more often found peripherally. Both subtypes have the potential to spread to regional lymph nodes, liver, bone, and brain [3]. There are limited studies on childhood bronchial carcinoids, although surgical resection has reported favorable outcomes, particularly for typical carcinoids. Atypical carcinoids, however, exhibit aggressive behavior in adults, but their incidence and prognosis in children remain poorly understood [4].

A review of published pediatric cases indicates that surgery is predominantly the primary treatment modality, leading to favorable survival outcomes in many reports. For instance, Rizzardi et al. [5] detailed the experiences of 15 pediatric patients; only one did not survive due to metastasis. Similarly, Geramizadeh et al. [6] documented positive outcomes in the majority of their cases, excluding two patients who succumbed to metastases. Despite these mortalities, the overall prognosis for bronchial carcinoids in pediatric patients remains generally encouraging, as Rojas and colleagues [7] noted a 95% overall survival rate in a sample of 133 individuals. The collected data underlines the critical role of early detection and intervention, an approach employed in our case management.

Carcinoid tumors typically manifest as polypoid masses within the bronchial tree, involving intraluminal, mural, and extrabronchial extensions. These can result in complete bronchial obstruction, which presents with respiratory symptoms such as shortness of breath and sibilant breath sounds. More severe repercussions, like lung collapse and obstructive pneumonia, may also occur. Symptoms like cough, dyspnea, and stridor, which are common in respiratory infections and pneumonia, can result in delayed diagnosis and treatment. Endobronchial growth often mimics bronchial obstruction and is frequently initially misdiagnosed as asthma [1]. In our case, the patient had been experiencing intermittent dyspnea over the past year, intermittent use of inhaled corticosteroids, and had undergone two recent treatments for pneumonia within the last month.

Radiological imaging plays a pivotal role in the diagnostic process, and atelectasis is the most commonly observed finding on chest X-rays. However, around 10% of cases might present with a normal chest X-ray. CT is crucial for detecting endobronchial lesions and lymphadenopathy; nonetheless, bronchoscopy remains the gold standard procedure for diagnosis, relieving obstructive symptoms, and attaining histopathological confirmation through a biopsy, as exemplified in our case [8].

In cases of suspected bronchial carcinoid, additional imaging with Ga-DOTA-TATE-PET should be undertaken to evaluate lymph node involvement and/or secondary tumors in distant sites [1]. For non-metastatic tumors, complete surgical removal is the preferred treatment, with lymph node excision recommended for atypical carcinoids due to their increased susceptibility to malignant transformation [2].

The aim of surgical treatment is the complete excision of the lesion while preserving as much of the parenchyma as possible. The anticipated outcome is generally favorable, with an 82% 10-year survival rate [3]. This aligns with the larger body of literature on pediatric bronchial carcinoid tumors, which indicates overwhelmingly positive outcomes following surgery, as reported in numerous studies. For instance, Hancock et al. [9] detailed three pediatric cases, all of which survived post-surgery. Gaissert et al. [10], and Al-Qahtani et al. [11] reported similar recovery rates, noting 100% survival in their patient populations.

Cryotherapy is often used as a safe and effective supplementary therapeutic approach for localized endoluminal typical carcinoid tumors. The high sensitivity of carcinoid tumors to freezing and the preservation of tracheobronchial cartilage tissue provides advantages over other adjunct therapies, minimizing local recurrences and long-term complications such as bronchial stenosis, which can occur with alternative adjunct therapies. Evidence of successful results has been shown with adjunct cryotherapy following bronchoscopic resection in adult

studies by Bertoletti et al. [12]. In our case study, adjunct cryotherapy was administered following bronchoscopic resection, and no recurrence was identified in follow-up bronchoscopies.

Conclusion

Although rare in childhood, bronchial carcinoids should still be considered during the diagnostic evaluation of children presenting with persistent pneumonia episodes or wheezing. Early diagnosis and management are crucial. Imaging and bronchoscopy play key roles in both the diagnostic and therapeutic approaches.

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