บทความฟื้นวิชาการ
Review Article

ยากันชักเหนี่ยวนำให้เกิดความผิดปกติทางสายตา

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บทคัดย่อ

โรคลมชัก คือ โรคความผิดปกติทางสมองซึ่งนำไปสู่การเกิดภาวะแทรกซ้อน ยากันชักมีบทบาทที่สำคัญใช้ในการรักษาโรคลมชัก อย่างไรก็ตาม ยากันชักเป็นยาที่มีดัชนีการรักษาแคบและไม่เฉพาะเจาะจงต่อเซลล์ประสาทที่ก่อให้เกิดการชักเท่านั้น ยานี้อาจมีผลต่ออวัยวะอื่นๆ เช่น เหนี่ยวนำให้เกิดความผิดปกติทางการมองเห็น ซึ่งปัจจุบันข้อมูลมีค่อนข้างจำกัด กลไกการเกิดยังไม่ชัดเจน บทความนี้นำข้อมูลที่เกี่ยวข้องกับการเกิดความผิดปกติทางการมองเห็นจากการได้รับยาในขนาดการรักษาและวินิจฉัยกลไกที่อาจเป็นสาเหตุของการเกิดในแต่ละอาการ คาดว่าข้อมูลนี้จะเป็นประโยชน์ต่อบุคลากรการแพทย์ในการดูแลผู้ป่วยโรคลมชักและเข้าใจการเกิดความผิดปกติทางการมองเห็น

คำสำคัญ : โรคลมชัก, ยากันชัก, ความผิดปกติทางการมองเห็น, ขนาดยาที่ใช้ในการรักษา

Antiepileptic drug–induced visual disturbances

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Abstract

Epilepsy is a type of neurological disorder that leads to complications if left untreated. Antiepileptic drugs (AEDs) play an important role in the treatment of epilepsy. However, because of their narrow therapeutic properties and as they are nonspecific to epileptic neurons, these agents can affect other organs. Although reducing the visual side effects of AEDs is crucial, there is presently limited related research data. In particular, the mechanism of antiepileptic-drug-induced visual disturbances is still unclear. This review focused on the visual disturbances associated with therapeutic doses of AEDs, and it explored the possible mechanisms of each symptom. This information will be useful to healthcare professionals' understanding of the visual complaints found in epilepsy patients.

Keywords : Epilepsy, Antiepileptic drugs, Visual disturbance, Therapeutic doses

Introduction

Epilepsy care is complex. Some patients need multiple antiepileptic agents to control their seizures. Visual disturbances among antiepileptic drug users are important but mostly unrecognized. The causes of visual disturbance may be related to the mechanistic properties of the drug. Moreover, Visual disturbance have been reported with varying prevalence. Some visual side effects resolve after medication discontinuation, others are dose related, while still others are progressive and eventually result in a permanent deficit.

AEDs are the main medication for treatment patient with epilepsy. The most AEDs have multiple mechanisms which include modulation of voltage-gated ion sodium and calcium channels, enhanced inhibition of neurotransmitter γ-aminobutyric acid ($GABA_A$ and $GABA_B$) and excessive excitatory neurotransmission mediated by glutamate and other excitatory amino

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acids.[1-3] Nowadays, several AEDs used to treat nonepileptic central nervous system disorders such as bipolar disorder, migraine and neuropathic pain.

Mechanism of antiepileptic drug–induced visual disturbance

Glutamate and gamma-aminobutyric acid (GABA) are the major excitatory and inhibitory neurotransmitters, respectively, in the retina of vertebrates. They play important roles in the processing of visual information, the regulation of neurogenesis, and neural stem-cell proliferation.[1] The functional families of GABA receptors in the retina and the central nervous system are GABA-A, GABA-B, and GABA-C. The GABA-A and GABA-C receptors are enriched in the retina and differentially expressed on the dendrite and axon terminals of both ON and OFF bipolar cells. The binding of GABA on its receptor triggers the opening of chloride channels, which induces inhibitory effects.

The functional sites of action for antiepileptic drugs (AEDs) enhance inhibitory neurotransmission that consists of an increase in GABA-mediated chloride conductance, a rise in the GABA level as a result of stimulation of the enzyme glutamic acid decarboxylase (GAD), an increase in the release of GABA, and the inhibition of the reuptake and degradation of GABA. Several processes associated with AEDs may enhance inhibitory neurotransmission (Figure 1).[2,3]

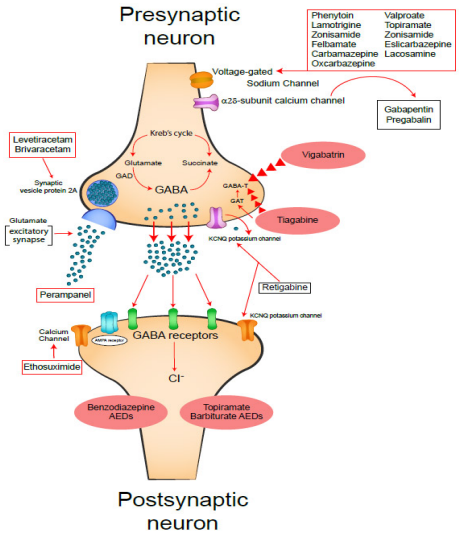

Figure 1 Mechanism of antiepileptic drugs[3]

Nystagmus and ophthalmoplegia

Ophthalmoplegia is the paralysis of one or more extraocular muscles, and it results in diplopia. Nystagmus is an abnormal, repetitive, uncontrolled eye movement. Acquired nystagmus typically develops in late childhood or adulthood. It often results in reduced vision perception and impaired coordination. These abnormal eye movements may be iatrogenic, with some being caused by the use of AEDs.

Sodium channel blockers are well-known as antiepileptic agents that cause nystagmus. Mild horizontal nystagmus has been observed even with therapeutic doses of phenytoin.[4] There have been 2 case reports of patients who developed reversible downbeat nystagmus that was related to the sodium channel blocking mechanism of AEDs. In Case 1, a 30-year-old man took multiple AEDs for refractory epilepsy: lamotrigine (300 mg), valproic acid (1200 mg), gabapentin (3600 mg), and carbamazepine (1200 mg). He developed downbeat nystagmus. After his physician reduced the lamotrigine dose, the downbeat nystagmus disappeared. In Case 2, a 38-year-old woman who had been taking lacosamide (200 mg), valproic acid (2000 mg), levetiracetam (2000 mg), and (lamotrigine 200 mg) presented with downbeat nystagmus and ataxia. Following discontinuation of the lacosamide, the downbeat nystagmus disappeared[5]. There was also a case report of a 42-year-old man taking only one AED who presented with nystagmus. He had been prescribed a dosage of carbamazepine of 800 mg/day. Following his unintentional double dosing, he presented with dizziness and blurred vision. A neurological examination revealed gaze-evoked nystagmus[6]. In another case report, phenytoin was found to have caused ophthalmoplegia while within the acceptable-dose range (Table 1)[7]. The mechanism of action of phenytoin is unclear. Cerebellar Purkinje cells have an inhibitory role in the vestibulo-ocular reflex. Given that phenytoin augments the rate of Purkinje discharge[8], the inhibitory effect in the vestibulo-ocular reflex may be enhanced, which interrupts the normal function of the reflex.

Other research suggested that the association between downbeat nystagmus and sodium-channel-

blocking AEDs might be explained by the expression of voltage-gated sodium channels Nav 1.1 and Nav 1.6, or by the primary voltage-activated sodium channel isoforms in cerebellar Purkinje neurons[9].

Diplopia may be a warning sign of a vision-threatening or life-threatening neurological disease. While diplopia is generally classified as monocular diplopia, which means the double vision occurs in one eye, the pathology locates in the eye globe and binocular diplopia that means the double vision was occurred because the misalignment of each eye. Binocular diplopia results from disruption of the extraocular muscles, which are innervated by oculomotor nerves, trochlear nerve and abducen nerves . Monocular diplopia mostly results from ophthalmological conditions, such as lens or corneal problems[10].

Because of the multiple mechanisms of diplopia, multiple antiepileptic agents can cause the condition. However, the specific AEDs inducing diplopia and the dose-response effect of individual drugs remain debatable.

A meta-analysis investigated the effects of second-generation AEDs on diplopia. The analysis showed that 8 second-generation AEDs could cause diplopia. In descending order of risk, as indicated by their odds ratios (ORs), the drugs were oxcarbazepine (OR 7.99; 95% CI 3.834–16.676); levetiracetam (OR 7.47, 0.375–148.772); lamotrigine (OR 5.23, 3.366–8.213); vigabatrin (OR 3.56, 1.143–11.096); pregabalin (OR 3.05, 1.531–6.068); topiramate (OR 2.66, 1.468–4.819); gabapentin (OR 1.97, CI 0.919–4.206); and zonisamide (OR 1.41, 0.713–2.773).[11] Moreover, lamotrigine was found to produce diplopia when the co-administration of lamotrigine and carbamazepine resulted in acute toxicity. High doses of lamotrigine were also found to lead to diplopia.[12]

Color disturbance, optic neuropathy

Optic neuropathy leads to vision loss. Its main clinical manifestations are visual field defects and dyschromatopsia. The characteristics are classified as rapid and gradual onset. The rapid onset form typically has demyelinating, ischemic, and traumatic etiologies. In contrast, the gradual onset form usually has hereditary, toxin, or even drug-related causes.[13]

Dyschromatopsia is a deficiency in the perception of some shades of red, yellow, and green while contrast sensitivity defines the threshold between visible and invisible.[14] The most common form of color disturbance is a red-green color vision defect. A less common, but more severe, form of color disturbance is blue cone monochromacy; which causes very poor visual acuity and severely reduced color vision. The causes of dyschromatopsia are gene mutations, nonhereditary conditions, and exposure to drugs or chemical compounds.[15] In the case of AEDs have been found to be frequently associated with color disturbance: phenytoin (77% of cases),[16] and carbamazepine (67% of cases; Table 1).[17] Color vision studies using the Farnsworth–Munsell 100-hue test were able to detect AED-toxicity-related dyschromatopsia. The research showed that patients treated with phenytoin or carbamazepine developed a blue-yellow color vision deficiency.[18] Vigabatrin (a GABA-transaminase inhibitor) is another AED that may induce a blue-color defect.[19,20] While contrast sensitivity tests seem to be abnormal in vigabatrin patients compared with sodium-channel-inhibiting AEDs partents.[21]

A visual field defect is another well-known side effect of vigabatrin. This AED may induce either a central or concentric visual field defect. Unfortunately, the condition is mostly not reversed after cessation of the medication (Table 1).[22,23]

There was a case report of a 12-year-old male with tonic movements and cerebellar ataxia who had been treated with phenobarbital (60 mg/day) and dantrolene. Over 12 months of treatment, his vision became blurred bilaterally. An ophthalmological examination revealed the presence of a central scotoma in the left visual field and a slight concentric constriction in the right visual field. After the phenobarbital was discontinued, his visual field completely recovered.[24]

There was also a rare case of carbamazepine-induced optic neuropathy presenting in a 15-year-old boy with conduct disorder. Treatment with carbamazepine (controlled release; 200 mg/day) was initiated, and for the following 3 days, an escalated dosage of 400 mg/day was administered. After 4 days of the carbamazepine regimen, however, the boy developed difficulty identifying colors and difficulty with his vision. The physician stopped the carbamazepine, and the boy's vision improved markedly.[25] The mechanism of the carbamazepine was unclear.

Glaucoma

Glaucoma is a progressive optic neuropathy. It results from an increase in intraocular pressure, which in turn stems from an imbalance in the secretion and drainage of aqueous humor.[26] Characterized by optic nerve cupping, glaucoma frequently leads to irreversible blindness. Glaucoma can be classified into open-angle glaucoma and angle-closure glaucoma. The related factors are age, family history, ethnicity, and background medical conditions.[26] Topiramate acts via several mechanisms, namely, sodium/calcium action potential modulation, GABA enhancement, and carbonic-anhydrase inhibition, which can be used to decrease intracranial pressure.[27,28] An acute angle-closure glaucoma crisis is characterized by a sudden blockage of the trabecular network.[29] Topiramate has been also reported to be associated with acute angle-closure glaucoma. The mechanism that was proposed was ciliochoroidal effusion, with displacement of the lens-iris diaphragm anteriorly and anterior chamber shallowing.[30,31] The carbonic-anhydrase inhibitor may explain these effects as similar as acetazolamide can do.[32,33] Glaucoma can begin to develop within a few weeks of the initiation of topiramate. The drug should be discontinued immediately if glaucoma is detected (Table 1).[34-36]

There have been three reports of AED-induced glaucoma. Two studies have described cases of angle-closure glaucoma that were related to topiramate and a sulfonamide derivative. In the case of topiramate, the reported onsets of angle-closure glaucoma mostly occurred during the first 2 weeks of treatment. However, the appearance of the topiramate-related reactions ranged widely, from several hours to 7 weeks after the initiation of the therapy (Table 1).[30] As to the sulfonamide derivative, there was a case report of zonisamide inducing angle-closure glaucoma and myopic shift. After 2 weeks of treatment with zonisamide for refractory migraines, a 39-year-old woman experienced sudden vision loss in both eyes, with a concurrent, bilateral, frontal headache. Her anterior chamber angles were narrow, and a gonioscopy examination confirmed partially occluded angles in both eyes. After the zonisamide was discontinued, full recovery was achieved.[37] Previous studies revealed that sulfonamide medications were associated with angle-closure glaucoma. The mechanism proposed was an idiosyncratic reaction of the sulfa-derivative in the uveal tissues. This was associated with an expansion of the extracellular tissues of the ciliary body and choroid (Table 1).[38]

Visual hallucinations

Visual hallucinations are defined as the perception of an object or an event in the absence of real, external stimuli.[39] Conditions that present with visual hallucinations are psychoses, delirium, dementia, seizures, Charles Bonnet syndrome, and Anton syndrome. Neurological disorders and medications also cause visual hallucinations.[39]

Gabapentin and pregabalin, both of which are GABA analogues, were reported to cause visual hallucinations. In case report, gabapentin (1800 mg once daily) was initiated for the treatment of neuropathic pain in a 65-year-old woman. After 1 month of therapy, she began to experience visual hallucinations 2 or 3 times per month. Despite her physician decreasing the gabapentin dosage to 300 mg once daily, she continued to have hallucinations once a week. However, once the physician discontinued the gabapentin, the woman no longer experienced visual hallucinations.[40] In another case report, a 36-year-old female suffering from anxiety was started on pregabalin (150 mg once daily), with the dose rapidly titrated to 150 mg three times a day. After 3 or 4 days, she reported having visual hallucinations and becoming increasingly agitated. Both gabapentin and pregabalin bind to the alpha-delta auxiliary subunit of the presynaptic voltage-gated calcium channels in the central nervous system. This binding then attenuates the depolarization-induced calcium influx at the nerve terminals. In turn, the influx of calcium reduces the release of excitatory neurotransmitters, such as glutamate, noradrenaline, and substance P. The reduction of glutamate levels may lead to hallucinations and other psychotic symptoms.[41]

Conclusions

Because the visual sequalae of AEDs may present even in the therapeutic range, they are usually unrecognized and likely to have serious side effects. As their mechanisms are still mostly unclear, a causal relationship between the visual side effects and AEDs is difficult to establish in clinical practice. The class and dosage of AEDs should be evaluated when epilepsy patients complain of any visual symptoms. More research, especially in basic pharmacology, is needed.

Declaration of conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Table 1 Summary of antiepileptic-drug induced visual disturbances

Antiepileptic drug	Mechanism of action[3]		Visual disturbances							
	GABA	Non-GABA	Diplopia	Nystagmus	disturban	Blurred vision	Glaucoma coma	hallucination	Optic neuropathy	Others data
1st generation										
Benzodiazepine[42-44]	– Activation of inotropic GABA-A receptor and enhanced response to synaptically released GABA	–	✓	✓	–	–	–	–	–	Diazepam attenuated on the human electroretinogram
Phenobarbital[24,45]	– Direct activation of the inotropic GABA-A receptor in the presence and absence of GABA	– Prolonged chloride-channel response to GABA – Reduced synaptic responses to glutamate – Blocked voltage-activated calcium channel	✓	✓	–	–	–	–	✓	
Phenytoin[16,46-49]		– Inhibition of voltage-gated sodium channels	✓	✓	77%	✓	–	✓	–	Phenytoin toxicity presenting with acute visual loss
Primidone[50,51]	– Direct activation of the inotropic GABA-A receptor in the presence and absence of GABA		✓	✓	–	–	–	–	–	
Carbamazepine[6,17,25,52]		– Inhibition of voltage-gated sodium channels	5%	✓	67%	5%–6%	–	–	✓	
Sodium valproate [53,54]	– Enhanced GABA turnover by increased synthesis or release of neurotransmitter		16%	1%–8%	33%	8%	–	–	–	

Antiepileptic drug	Mechanism of action[3]		Visual disturbances							
	GABA	Non-GABA	Diplopia	Nystagmus	disturban	Blurred vision	Glaucoma coma	hallucination	Optic neuropathy	Others data
2nd generation										
Vigabatrin[20,55-57]	– Altered GABA turnover by inhibition of mitochondrial enzyme GABA-transaminase		✓	✓	✓	✓	–	–	–	Visual field defect
Oxcarbazepine[58-60]		– Inhibition of voltage-gated sodium channels – Inhibition of low-voltage activated (LVA) T-type calcium channel	1%–40%	2%–26%	–	1%–4%	–	–	–	Toxic to retinal glia cell in rats
Lamotrigine[12,61]		– Inhibition of voltage-gated sodium channels – Inhibition of calcium channel	24%–49%	2%–5%	–	11%–25%	–	–	–	Lamotrigine-treated visual snow
Gabapentin[40,62-64]	– Enhanced GABA turnover by increased synthesis or release of neurotransmitter	– Direct inhibition of voltage-gated calcium channel, resulting in glutamate release	1.2%–5.9%	–	–	✓	–	✓	–	Visual field constriction
Felbamate[65,66]	– Potentiated agonist	– Inhibition of NMDA subtype glutamate receptor – Influence on HVA calcium channel conductance – Inhibition of voltage-gated sodium channels	3.4%–6.1%	✓	–	-	–	–	–	
Topiramate[30,67-69]	– Potentiated GABA agonist	– Influence on HVA calcium channel conductance – Blockage of AMPA receptor – Inhibition of voltage-gated sodium channels	1%–10%	10%	–	✓	2 reports	–	–	Visual field defect (0.1%–1%); myopia

Antiepileptic drug	Mechanism of action[3]		Visual disturbances							
	GABA	Non-GABA	Diplopia	Nystagmus	disturban	Blurred vision	Glaucoma coma	hallucination	Optic neuropathy	Others data
Tiagabine[70]	– Altered GABA turnover by prevention of removal of GABA from the synaptic cleft		–	–	–	✓	–	–	–	Visual field defect (0.1%–1%); myopia
Levetiracetam[71-73]		– Inhibition of both N and P/Q-types of the HVA calcium channel – Inhibition of the synaptic vesicle protein 2a (SV2a)	2%	-	✓	✓	–	✓	–	
Pregabalin[41,74]	– Enhanced GABA turnover by increase in neuronal GABA concentrations	– Direct inhibition of voltage-gated calcium channel, resulting in glutamate release	2%–9%	–	–	10%	–	–	–	Visual field defect
Zonisamide[37,75,76]		– Inhibition of voltage-gated sodium channels – Inhibition of low-voltage activated (LVA) T-type calcium channel – Inhibition of carbonic anhydrase	6%	4%	–	–	1 report	✓	–	
Stiripentol[77,78]	– Potentiated GABA agonist (selectivity for alpha3-beta3-gamma2 containing receptors)		-	–	–	–	–	✓	–	–
3rd generation										
Perampanel[79]		- Non-competitively selected antagonizing of AMPA glutamate receptor	1%–5%	–	–	1%–4%	–	–	–	
Lacosamide[11,80]		– Inhibition of voltage-gated sodium channels	5%–8%	–	–	9%–11%	–	✓	–	
Eslicarbazepine[81]		– Inhibition of voltage-gated sodium channels	9%–10%	1%–2%	–	5%–6%	–	–	–	Visual impairment(1%–2%)

Abbreviations: AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, gamma-aminobutyric acid; HVA, high-voltage-activated; NMDA, N-methyl-D-aspartate

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