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CASE REPORT

VALPROIC ACID FOR REFRACTORY POST-TRAUMATIC DIZZINESS AND PHOTOPSIA

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Abstract

Introduction: Post-concussion syndrome (PCS) is a collection of cognitive, vestibular, and visual symptoms that may persist after mild traumatic brain injury (mTBI). Current management is largely supportive, highlighting the need for alternative pharmacologic approaches. This case report explores the therapeutic potential of valproic acid (VPA), a compound with neuroprotective and anti-inflammatory effects.

Case Presentation: A 28-year-old woman presented with persistent vertigo and visual disturbances, including photopsia, following a mild head injury sustained in a motor vehicle accident. Neurological examination and imaging were unremarkable. Symptomatic therapies provided only partial and temporary relief, prompting the trial of VPA. The patient subsequently experienced gradual clinical improvement, achieving complete symptom resolution within six months and maintaining remission after discontinuation of treatment.

Discussion: The patient's symptoms were attributed to functional disturbances involving the occipital cortex and vestibular pathways, commonly implicated in PCS. Hypothesized contributors included ionic disequilibrium, cortical hyperexcitability, and neuroinflammatory processes. Beyond its traditional use as an antiepileptic, VPA may offer therapeutic advantages in PCS through GABAergic modulation, Histone Deacetylase (HDAC) inhibition, and anti-inflammatory actions.

Conclusions: This case highlights VPA as a promising pharmacologic option for refractory PCS. However, further studies are required to determine its efficacy, optimal dosage, and safety profile in this setting.

Keywords: Post-Concussion Syndrome; Valproic Acid; Mild Traumatic Brain Injury; Vestibular Symptoms; Visual Dysfunction

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Introduction

Post-Concussion Syndrome (PCS) refers to a variety of physical, cognitive, behavioral and emotional symptoms that emerge following a traumatic brain injury (TBI) [1]. A concussion is a form of mild traumatic brain injury that results in physiological disturbances in brain function, despite the absence of visible structural damage on CT or MRI scans [2]. PCS most commonly develops in individuals with mild TBI (mTBI), it can also arise following TBI of any severity [3]. Individuals with a history of mTBI can experience PCS such as persistent headaches, tiredness, visual disturbance, balance problems, disorientation, dizziness, sleep disturbances,

neuropsychiatric issues, and trouble focusing or concentrating [4]. The reported prevalence of PCS following mTBI varies widely. While some studies suggest that around 10-15% of individuals with mTBI develop PCS, others report rates as high as 35.4% [5,6] Previous studies have shown that most common symptoms indicating PCS were difficulty concentrating (37,5%), light sensitivity (32,1%), headaches (30,3%), frustration (23,2%), post-traumatic stress disorder (22,3%), dizziness (20,5%), irritability (18.7%), depression (16,9%), sleep disturbance (16,1%), memory problems (16,1%), anxiety (14,3%), blurred vision (10,7%), and double vision (7,1%)[4].

TBI is the major risk factor of developing dizziness and balance issues among the patients admitted in emergency department. Another study stated that dizziness is the second most common complaint among patients with mTBI, which may stem for either non vestibular factors or central and peripheral vestibular origins [7]. Approximately 17% of individuals TBI experience post-traumatic dizziness, with recurrence reported in 9 patients (40.9%). Dizziness affects about 46% of TBI patients overall [8]. The injury may lead to vestibular hypofunction and swelling of the vestibular labyrinth, disrupting signals from the vestibular nucleus and resulting in dizziness, balance disturbances, and benign paroxysmal positional vertigo (BPPV) [7,9]. Since over half of the brain's pathways are involved in vision and eye movement regulation, a widespread brain injury like a concussion frequently also impacts the visual system [10]. Studies have shown that visual impairments can affect up to 69% of individuals after experiencing a mild traumatic brain injury [11]. Research involving both adolescent and adult patients has identified ongoing visual system disturbances following a concussion [12]. These can include double vision (diplopia), reduced visual attention, irregular pupil responses, and increased abnormal eye tracking movements [11].

Due to the wide range of variation in the onset, duration, and severity of symptoms, there are no universally established, evidence-based protocols for managing post-concussion syndrome. Treatment approaches often differ depending on the provider's experience and the specific setting. Nevertheless, some general principles can still guide the management of PCS. Post-concussion syndrome (PCS) management involves a holistic strategy that focuses on rest, gradual return to daily activities, effective symptom control, avoiding activities that worsen symptoms, all customized to suit each patient's specific needs [2]. Patients with PCS are given pharmacological treatment based on the symptoms they experience but medications are not the cornerstone of post concussion therapy [13,14]. Current treatments for post concussion syndrome are primarily supportive, as there are no clinically available cytoprotective therapies that directly reduce cell death or enhance recovery [13]. One potential therapeutic candidate is valproic acid (VPA), an anticonvulsant commonly used to treat epilepsy and mood disorders; it has both neuroprotective and anti-inflammatory properties [15]. However, there is currently limited research investigating the use and effectiveness of VPA in managing PCS. This

study aims to report the usefulness and effectiveness of VPA in a case of PCS.

Case Presentation

A 28-year-old female, weighing 50 kg, presented to the Emergency Department approximately 15 minutes following a motor vehicle accident, in which her head hit the asphalt, with chief complaints of acute onset severe vertigo. The patient described an intense spinning sensation accompanied by blurry vision in the left eye and the perception of floating, worm-like entoptic phenomena. She experienced six episodes of projectile vomiting. There were no accompanying complaints of limb weakness, paresthesia, loss of consciousness or seizure. No prior medical or neurological history. Upon initial evaluation, patient's GCS score was 15/15, followed by her vital signs: blood pressure 165/110 mmHg, heart rate 114 bpm, respiratory rate 21 breaths per minute, oxygen saturation 100%, body temperature 36.8°C, and blood glucose level 90 mg/dL. Neurological examination, such as head impulse test, nystagmus assesment and test of skew proved negative results. A laceration measuring 5 × 2 × 1.5 cm with active bleeding was identified in the occipital region.

Cranial computed tomography (CT), chest radiography, and lumbosacral X-ray imaging revealed no abnormalities. The patient was treated in the Emergency Department with analgesia (metamizole) and diphenhydramine. Following three days of inpatient observation and treatment, her condition stabilized and she was discharged. However, two days later, she presented herself to the neurology outpatient clinic with persistent dizziness and continuous photopsia in both eyes throughout the day. A comprehensive ophthalmologic examination demonstrated normal ocular structure and function. Patient received pharmacologic management included betahistine, flunarizine, dexamethasone, and ondansetron. Patient wasn't introduced to vestibular exercises thus patient didn't do any. Patient also wasn't educated on salt and caffeine restriction. After two weeks of treatment, there was no significant improvement in either dizziness or visual complaints.

Electroencephalography (EEG) was performed and revealed normal findings. Informed consent was obtained from the patient to participate in a new experimental therapeutic regiment for PCS. The therapeutic regiment was then adjusted to include valproic acid (VPA) 250 mg twice daily. At the one-month follow-up, the patient reported symptomatic improvement, with visual flashes decreasing from constant to approximately every two hours.

Therapy was continued. By the second month, dizziness was reported only in the premenstrual phase, and photopsia episodes were limited to 3–5 times daily. In the fourth month, the patient discontinued therapy, resulting in symptom recurrence during menstruation. Treatment was resumed, and by the sixth month, VPA was tapered to 250 mg once daily, with complete resolution of symptoms. At the seventh month, medication was stopped entirely, with no recurrence of dizziness or visual symptoms thereafter.

Figure 1. 5 x 2 x 1.5 cm laceration in occipital region (yellow arrow)

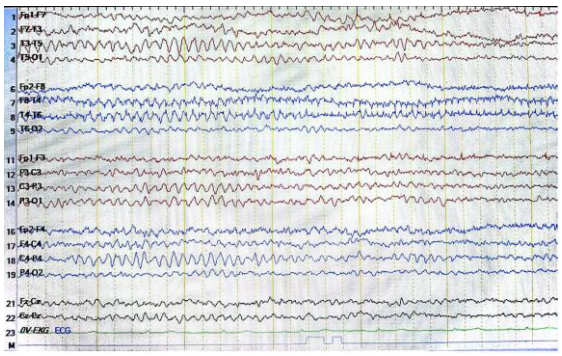

Figure 2. Electroencephalography showed no abnormality

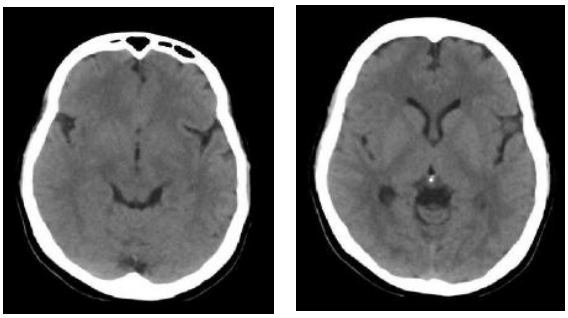

Figure 3. Axial images of cranial CT scan showed no abnormality

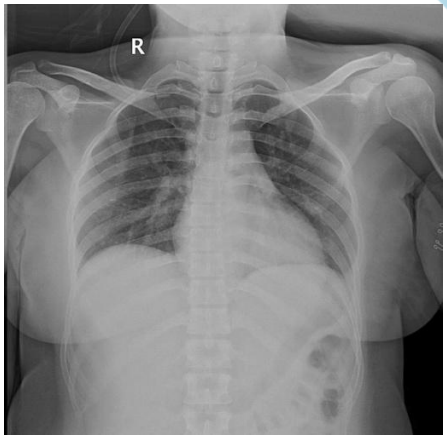

Figure 4. Chest X-ray showed no abnormality

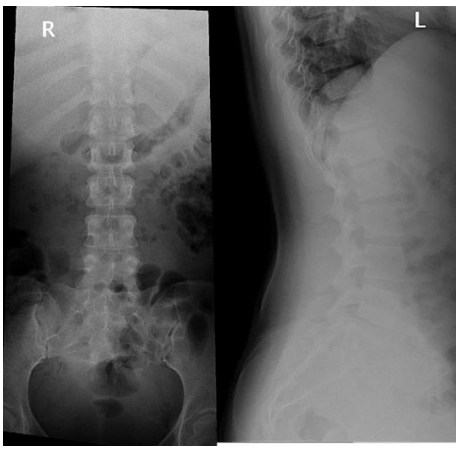

Figure 5. Lumbar X-ray showed no abnormality

Discussion

The World Health Organization (WHO) defines PCS as the occurrence of three or more of the following symptoms following a head injury such as headache, dizziness, fatigue, irritability, sleep disturbances, difficulty concentrating, or memory problems [16]. TBI affects around 69 million people globally each year, with most cases classified as mTBI [17]. Despite their classification, approximately 10–25% of individuals with mTBI continue to experience post-concussion symptoms over an extended period, a condition commonly known PCS and can lead to

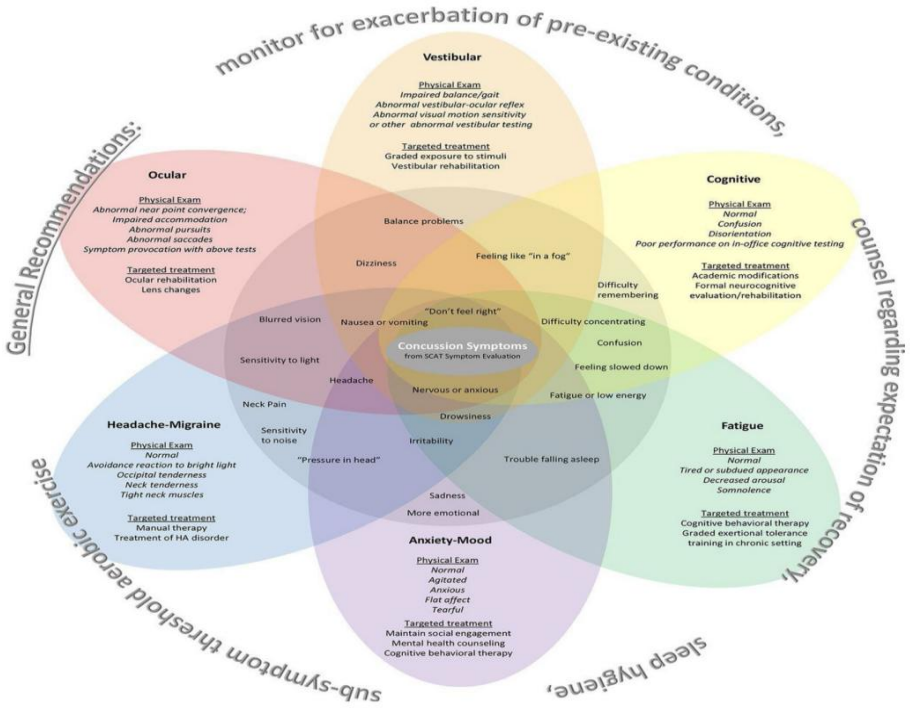

Figure 6. Common Post Concussive

complex brain responses and result in persistent PCS in 10–30% of cases [18].

Some individuals experience acute post-concussion symptoms including physical symptoms (nausea, dizziness, headaches, blurred vision, hearing disturbances, and fatigue), cognitive issues (problems with memory and executive function), emotional, and behavioral disturbances (emotional instability and disinhibition)[14,18]. Previous study stated that headache is the most common and long-lasting symptom after a concussion, often persisting for over a year. If it worsens within seven days of ‹the injury, it is classified as a posttraumatic headache (PTH), typically resembling a migraine [14] Balakrishnan et al. examined various categories of PCS symptoms, including somatic complaints, emotional changes, cognitive issues, post-symptoms, psychosocial-behavioral aspects, and pre-symptoms. At the initial follow-up (two weeks post-injury), somatic symptoms (headache, malaise, fatigue, noise intolerance, and dizziness) were reported by all PCS patients (100%) and were the most prevalent [5] Cognitive impairments were the second most commonly affected symptom category [5]. Harmon described the symptoms commonly experienced by patients with PCS in Fig.4, the illustration shows that many of the common symptoms overlap in terms of clinical presentation and management approach [19].

The brain is the most complex and largest organ in the human body, made up of distinct regions that function collaboratively. These regions are organized into various lobes and protected by a tissue layer called the meninges. Each region of the brain plays a specific role in controlling different bodily functions. Every concussion is distinct, influenced by variations in the strength, direction,

rotation, and origin of biomechanical forces involved in the injury. This variability explains the unpredictable nature of post-concussion symptoms, which can appear and disappear in varying ways [20].

In this case report, the patient complained of a sudden onset of spinning dizziness that persisted continuously, vomiting without accompanying nausea, and the sensation of seeing several moving worm-like strands in the left eye shortly after the accident. The symptoms lasted for some time. This aligns with the previous research, which shows that 80–90% of head traumas are classified as mTBI, and such impacts can trigger complex neurometabolic and neuroinflammatory cascades that may develop into PCS, affecting 10–30% of mTBI [17]. A concussion, along with its associated symptoms, can progress into a long-term condition known as PCS. This chronic condition affects approximately 24% to 84% of individuals with mTBI and includes symptoms such as headaches, dizziness, fatigue, sensitivity to light or noise, sleep disruptions, and difficulty concentrating [21]

After a head injury, the brain experiences significant chemical and biological alterations. In cases of mTBI, the most frequent pathological mechanism involves the damage of neuronal axons and small blood vessels, results in reduced blood flow and oxygen supply to the brain (ischemia and hypoxia), triggering various chemical reactions that cause inflammation and swelling [22]. Following a concussion or mTBI, the brain undergoes ionic imbalance (sodium, potassium, and calcium ions) and excessive glutamate release, triggering NMDA receptor activation and calcium influx. This leads to the production of reactive oxygen species (ROS) which, when overproduced, can damage proteins and cell [23,24]. These chemical changes contribute to secondary injury, inflammation, and potential brain cell death. As these changes occur within the brain, the patient starts to experience a variety of symptoms resulting from their effects [24].

Based on the physical examination, the patient had a GCS score of 15 and was fully conscious. A laceration measuring 5 × 2 × 1.5 cm was found in the occipital region, accompanied by active bleeding. The symptoms experienced by the patient in this case occurred due to a concussion to the occipital region of the head. Initially, the patient complained of spinning dizziness and seeing a floating black line in the left eye resembling a worm. At a different time, the patient also reported seeing flashes of light in both eyes, this phenomenon, known as photopsia. The human visual cortex, primarily located in the occipital lobe, is divided into eight regions, including the primary (V1), secondary (V2), and several association areas (V3, V3a, V4, VP, MT, MST). The primary visual cortex lies near the calcarine sulcus, with other areas positioned around it, each responsible for processing different aspects of visual information [25].

The visual cortex plays a central role in receiving, interpreting, and processing visual signals that travel from the retina through the optic nerve and thalamus before reaching the primary visual cortex [25]. It handles various aspects of vision, including color, brightness, shape, and motion, and processes visual input on the

side of the brain opposite the eye. Damage to this area can lead to symptoms like headaches, dizziness, light sensitivity, balance issues, and visual disturbances [26,27]. Studies have shown that oculomotor and sensory impairments linked to the visual cortex may appear within the first week after a concussion and persist over time [25].

Photopsia, or the perception of flashing lights, is a frequent visual disturbance where individuals see brief flashes or star-like lights. It has a wide range of possible causes and requires careful evaluation to determine its origin [28]. Patients with mild traumatic brain injury (mTBI) often report photopsia. In the context of head trauma, the sensation of "seeing stars" is typically temporary and results from spontaneous neural activity in the occipital lobe, which the brain interprets as visual flashes[29,30]. Clinically, it is important to distinguish whether photopsia occurs in one or both eyes. Unilateral photopsia—flashes seen in only one eye—typically suggests a problem within the eye itself. Bilateral photopsia—flashes perceived in both eyes at once—usually indicates a central (brain-related) origin [28].

When photopsia is limited to one eye, a detailed eye examination and patient history are necessary. These flashes are often accompanied by floaters, or dark spots in the visual field, commonly caused by posterior vitreous detachment. In this condition, the gel-like vitreous pulls away from the retina, which can stimulate retinal cells and cause the perception of light flashes [31]. Small particles or blood may also be released, appearing as floaters [31,32]. Most of the time, this is a harmless process and floaters fade with time. However, if the pulling force on the retina is strong enough, it may result in a retinal tear, which can lead to a retinal detachment.

Balance relies on the vestibular system, sensory input, and vision [20]. Head trauma can disrupt these systems, especially the peripheral vestibular system, leading to dizziness or lightheadedness [33]. Vestibular dysfunction in post-concussion syndrome may result from direct injury or secondary brainstem and cortical damage, with peripheral causes being more common than central ones [34]. While dizziness after mTBI is often attributed to central brain dysfunction, research has shown it may also result from peripheral vestibular system damage [35]. This system includes two types of sensory organs: the three semicircular canals, which detect rotational head movements, and the otolith organs (utricle and saccule), which sense linear acceleration and head position relative to gravity [36]. The vestibulo-ocular reflex (VOR), which links vestibular input to eye muscles, can be evaluated using the caloric test—considered the gold standard for diagnosing peripheral vestibular dysfunction [37].

Peripheral vestibular loss can affect the superior and/or inferior branches of the vestibular nerve, as well as the semicircular canals and otolith organs. Advances in diagnostic tools, such as vestibular-evoked myogenic potentials (VEMPs), now allow assessment of otolith organ function. Studies have shown that 25–32% of individuals with post-concussion dizziness display abnormal cervical VEMPs (cVEMPs), indicating otolith

dysfunction [35,38]. Similar findings were observed in the previous study in veterans with mTBI, where about 30% showed unilateral otolith dysfunction [35,38].

Head trauma can dislodge the otoconia (calcium carbonate crystals in the otolith organs responsible for detecting gravity) from the utricle, allowing them to migrate into a semicircular canal and trigger benign paroxysmal positional vertigo (BPPV) [8]. BPPV is thought to be caused by canalithiasis, where free-floating otoconia in the semicircular canal's endolymph disturb fluid motion, activating vestibular sensory cells and resulting in vertigo and nystagmus [39]. In a study of 100 patients, it identified BPPV as the most frequent vestibular disorder post-head injury [35]. Research commonly identifies trauma as the cause in roughly 10% of patients. In a study conducted by Józefowicz-Korczyńska and colleagues involving 179 individuals with mild head injuries, 19 were diagnosed with BPPV, representing 10.6% of the participants [40]. In a study by Ernst et al., 63 patients experiencing vertigo following head or neck trauma were evaluated, and 36 of them (57%) were found to have developed BPPV within the first 24 hours post-injury [8].

The patient in this case underwent further evaluations of the head and eyes. Supportive diagnostic tests, including Electroencephalogram (EEG) and head Compute Tomography (CT), along with an ophthalmologic examination conducted by a specialist, revealed no significant abnormalities. Presently, clinical brain imaging (such CT, MRI, EEG) is unable to detect or confirm a concussion [18]. Its primary role is to rule out other conditions or injuries such as bleeding or brain contusions that might present with similar symptoms but necessitate different treatment approaches (1). There is currently no agreement on the prognostic significance of imaging findings in detecting brain abnormalities following mTBI [18].

Some research has demonstrated that MRI and magnetic resonance spectroscopy (MRS) can identify structural or functional brain changes in individuals whose CT scans appear normal [41]. CT often miss subtle injuries like mild TBI or diffuse axonal injury, which are better detected by MRI [41]. While MRI provides greater soft tissue detail and is more effective for identifying certain brain injuries, it is less practical in acute settings due to longer scan times, limited availability, and compatibility issues with medical devices [19]. These findings may help explain persistent post-concussion symptoms in certain patients. Thus, for some patients, persistence of post-concussion symptoms may be explained by yet unknown brain abnormalities .

Seizures are rarely linked to mTBI in the hyperacute phase, while posttraumatic epilepsy is more commonly seen in severe cases [2]. Although EEG has limited sensitivity for detecting mTBI, it may occasionally reveal focal or generalized slowing, which often lacks significant diagnostic utility [42]. EEG is more likely to detect abnormalities soon after the injury, but its use is often impractical in acute trauma settings [43]. Following mTBI, 86% of patients with neurological abnormalities also showed abnormal EEG results. However, only 23% of those with abnormal

EEGs had corresponding findings on neurological examination [44]. EEG findings vary among individuals, likely due to differences in injury severity, and in some cases. Conventional EEG is important for the evaluation of posttraumatic epilepsy but is not useful as a routine screening measure among individuals with mTBI or postconcussive symptoms [42].

Therapy initiations for PCS should be based on the patients' reported symptoms [45]. Different patients may report different kinds of symptoms. Symptomatology of PCS has been explained above. In this case, the patient reported persistent dizziness and continuous photopsia two days after being discharged or five days after the accident. From those symptoms, the neurologist prescribed her with betahistine, flunarizine, dexamethasone and ondansetron. This prescription was in line with the Indonesian Neurology Clinical Practical Guideline.

Usage of betahistine and flunarizine as vestibular suppressant is recommended to alleviate symptoms of benign paroxysmal positional vertigo [46]. Canalith repositioning therapy is also mentioned in the Indonesian guideline as well as some Canadian guidelines for PCS. Canadian guidelines recommend canalith repositioning maneuver or Epley maneuver to treat benign paroxysmal positional vertigo in PCS [45,47]. The patient didn't undergo Epley maneuver due to intense pain and unwillingness to cooperate. Complaints regarding visual disturbance or abnormalities should be handled by ophthalmologists [45,47]. The patient went through a complete ophthalmological examination and its result was normal.

After two weeks of therapy, the patient didn't feel better. She was still dizzy and kept on having floaters. The neurologist decided to add VPA 250 mg twice daily to her regiment of drugs. VPA is a derivative of valeric acid with an active compound called 2-propylpentanoic acid. In 1972, the US Food and Drug Administration approved its use to treat absence seizure. Next, in 1983, it was approved to treat complex partial seizures. Since then, VPA has become a common and renowned antiepileptic drug. Besides antiepileptic, there are several off-label applications such as migraine prophylaxis, manic episodes in bipolar disorder, postherpetic neuralgia and emergency treatment of status epilepticus [48].

According to the Indonesian Food and Drug Agency, recommended VPA dosage for therapeutic usage starts from 10-15 mg/kg/day and may be increased by 5-10mg/kg/week after one week interval. Doses above 60 mg/kg/day hasn't been proven it's safeness for patients. [49]

VPA's mechanism of action includes increasing levels of glutamatergic and γ-aminobutyric acid (GABA) in the central nervous system, suppressing histone deacetylase, and blocking voltage-gated ion channels. GABA is synthesized by using α-ketoglutarate through the Krebs cycle, then metabolized into succinate semialdehyde before being converted to succinate using GABA transaminase and succinate semialdehyde dehydrogenase. VPA inhibits GABA transaminase and succinate semialdehyde dehydrogenase, thus increasing GABA levels by reducing its

breakdown process. VPA also inhibits high-frequency neuronal activity via voltage-gated calcium, sodium, and potassium channels. HDAC has recently been proven to be blocked by VPA, specifically HDAC1, and also other HDAC. Histone deacetylase inhibitors may increase the interpretation of apoptosis and anticancer genes [50].

So far, VPA's application for TBI is still limited. Various research in animals show promising results. VPA effectively penetrates injured brain tissue and provides neuroprotective and pro-survival effects, leading to a significant reduction in lesion size following isolated TBI [51]. VPA-induced enhancement of autophagy and antioxidant responses is likely driven by increased activation of the Nrf2/ARE pathway, resulting from direct inhibition of HDAC3. This inhibition also dampens TBI-related microglial activation and the resulting inflammatory response, contributing to overall neuroprotection. Another research points out a different perspective in VPA's neuroprotective property. VPA exerts mild neuroprotective and anti-inflammatory effects, likely driven by beneficial systemic metabolic shifts that lead to elevated plasma lysophosphatidylcholines levels. These lysophosphatidylcholines are actively transported into the brain, where they serve as carriers for neuroprotective polyunsaturated fatty acids [15]. VPA demonstrates neuroprotective and anti-apoptotic effects in traumatic brain injury, primarily by upregulating the expression of AKT and ERK, signaling pathways known to mediate its protective actions. In both primary cortical neurons and SH-SY5Y cells, VPA reduces endoplasmic reticulum stress and enhances AKT activity, contributing to its anti-apoptotic and neuroprotective properties [50].

Previously, there hasn't been any research involving VPA administration to PCS human patients. This is the first study with the aim of investigating VPA administration to PCS human patients. Limitation of this study include low generalizibility due to single sample size and low possibility to determine causality between VPA and PCS In this case, the patient was given 250 mg of VPA twice daily for six months. After six months, the patient felt complete remission of symptoms. This proves VPA is effective to relieve PCS symptoms and might be administered for PCS patients. Further research and tests need to be conducted to understand more of VPA's potential in treating PCS. Research needs to be focused on trials regarding VPA's dosage and duration of therapy as well as VPA's mechanism of action in PCS patients.

Conclusion

This case illustrates the promising role of valproic acid in the treatment of post-concussion syndrome, particularly in patients who do not respond to conventional management strategies. In the case of a 28-year-old woman presenting with persistent vertigo and photopsia following a mild traumatic brain injury, standard interventions such as vestibular suppressants, corticosteroids, and symptomatic agents failed to produce meaningful clinical improvement. The subsequent introduction of valproic acid in combination with neurotrophic support led to gradual and sustained symptom

resolution, with complete remission achieved within six months. This feat may be achieved through valproic acid's neuroprotective and anti-apoptotic properties.

Although based on a single case, this observation underscores the potential of valproic acid as a therapeutic option for select individuals with post-concussion syndrome, especially those with persistent visual or migrainous symptoms unresponsive to first-line treatments. Further investigation through prospective studies and randomized controlled trials is essential to clarify its mechanisms of action, evaluate its efficacy across diverse clinical profiles, and establish its safety and long-term outcomes. This case adds to the emerging discourse on pharmacological strategies in post-traumatic neurorehabilitation and highlights the need to consider targeted, mechanism-based interventions in the management of complex concussion-related syndromes.

Conflict of Interest

The authors declared no conflict of interest.

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