Clinical Efficacy of Topiramate in the Treatment of Pediatric Idiopathic Intracranial Hypertension: Case Report

Pediatrik İdiyopatik İntrakraniyal Hipertansiyon Tedavisinde Topiramatın Klinik Etkinliği

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ABSTRACT There have been no sufficiently large studies of any treatment modality in idiopathic intracranial hypertension (IIH) in childhood. Therefore there is no consensus on treatment. Topiramate, a relatively new anticonvulsant, has also been considered for treating IIH. It has multiple mechanisms of action including inhibition of carbonic anhydrase at clinically relevant doses. It selectively, but not specifically, inhibits isoenzymes II and IV. It has also been shown in several studies to cause dose-dependent weight loss. The combination of carbonic anhydrase inhibition reducing cerebrospinal fluid production and appetite suppression which causes weight loss is the indication for the use of topiramate in the treatment of IIH. To the best of our knowledge, there is only one report which has shown the efficacy of topiramate in the treatment of IIH. We report three new pediatric cases with IIH who were successfully treated with topiramate. On the basis of the available evidence, topiramate appears an effective option for the treatment of pediatric IIH with variable clinical and therapy resistant cases.

Key Words: Topiramate; pseudotumor cerebri

ÖZET Çocukluk çağında idiyopatik intrakraniyal hipertansiyon tedavisi ile ilgili yeterince çalışma bulunmamaktadır. Bu nedenle tedavi konusunda bir fikir birliği yoktur. Yeni kuşak antiepileptik ilaçlardan topiramat idiyopatik intrakraniyal hipertansiyon tedavisinde denenmektedir Topiramatın uygun dozlarda karbonik anhidraz inhibisyonunu da içeren birçok etki mekanizması vardır. Spesifik değil ama selektif olarak izoenzim II ve IV'ü inhibe eder. Birçok çalışmada doz bağımlı kilo kaybına yol açtığı da gösterilmiştir. İdiyopatik intrakraniyal hipertansiyon tedavisinde topiramatın kullanım endikasyonu serebrospinal sıvı üretimini azaltması ile kilo kaybına neden olan iştahı baskılamasıdır. Şu ana kadar çocukluk çağında idiyopatik intrakraniyal hipertansiyon tedavisinde topiramatın etkinliğini gösteren tek bir bildiri bulunmaktadır. Bu yazıda, topiramat ile başarılı bir şekilde tedavi edilen üç pediatrik idiyopatik intrakraniyal hipertansiyon olgusunu sunduk. Bu bilgilere dayanarak, topiramat değişik klinik ve tedaviye dirençli pediatrik intrakraniyal hipertansiyon olgularında etkili bir tedavi seçeneği gibi görünmektedir.

Anahtar Kelimeler: Topiramat; psödotümör serebri

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Formerly termed benign intracranial hypertension, pseudotumor cerebri (PTC) or idiopathic intracranial hypertension (IIH) are the clinical syndromes of raised intracranial pressure without clinical, laboratory or radiological evidence of intracranial pathology.[1,2] Epidemiological data on childhood IIH, which limited to hospital based retrospective case series, vary from 0-0.9 per 100 000 children.[3]

The management of a proven IIH in children continues to cause debates as an ideal treatment has not been identified as yet. Various therapeutic measures have been used, however their therapeutic efficacy has not been verified in controlled studies.

Topiramate, a broadspectrum anticonvulsant, has been currently proposed in the treatment of IIH, but has been only rarely applied in this indication so far. To date, there are no published report to confirm the efficacy of topiramate in treating childhood IIH except from one case report.[4]

We report three children of IIH with variable etiologies and presentations who have been successfully treated with topiramate.

CASE REPORTS

CASE 1

A 13-year-old obese girl admitted to the emergency department with one month history of daily headache, dizziness and diplopia. The headaches lasted at least two hours, were bilateral, moderate to severe in intensity, sometimes dull, sometimes throbbing, and accompanied by blurred vision, diplopia, exercise intolerance, photophobia, and phonophobia. Headache did not give response to aspirin or paracetamol. She was not taking any other medications. There was no family history of migraine or other types of headaches. Her body weight was 97 kg (>97 percentile), height 165 cm (50 percentile) and a body mass index of 33.1. Physical examination was normal except bilateral papilledema (stage 1 papilledema, according to the Lars Frisen grading scale). Both visual acuity and visual fields were normal. Routine laboratory determinations, as well as cranial magnetic resonance imaging (MRI) were normal. A lumbar puncture (LP) was carried out with unremarkable results. The cerebrospinal fluid pressure raised at 28 cm H_2O. The results of chemistry, microscopy, and cytology tests were normal.

Topiramate was initiated at a dose of 50 mg/day and gradually titrated to 200 mg/day. Headache, diplopia and papilledema completely resolved. At the time of this report, she had been on topiramate for 6 months with no significant headaches. A further positive effect of topiramate was a slight weight reduction. She lost 8 kg during six months of topiramate treatment. She did not develop any of the known side effects of topiramate.

CASE 2

A six-year-old boy presented to his general practitioner with a one-month history of persistent headache and blurred vision. He was subsequently referred to our department for neurological consultation. Initial physical examination was normal. He had reduced visual acuity in his right eye and bilateral swollen optic discs on fundoscopy. Cranial MRI and magnetic resonance angiography, including magnetic resonance venography, were normal. LP revealed high opening pressure (28 cm H_2O) with normal glucose (3.2 mmol/L) and protein (0.3 g/L) cerebrospinal fluid (CSF) concentrations. The diagnosis of IIH was made and the patient was started on acetazolamide treatment 50 mg/kg/day. During the subsequent three years, the patient's headaches and visual blurring had a sporadic pattern and responded temporarily to LPs performed every few months and revealed persistently high opening pressures (>30-cm H_2O) with normal glucose and protein CSF concentrations. In the follow up peripheral visual field loss occurred and headaches became refractory to acetozolamide and serial LP's. Occasionally he developed intermittent vomiting attributed to gastrointestinal causes.

After headache worsened and the patient had refused a further therapeutic LP, topiramate was initiated. Topiramate was started at a dose of 50 mg/day and increased by 25 mg every two weeks and a maintainance dose of 150 mg/day was reached. After one month with topiramate treatment, the patient reported nearly complete resolution of his headache. Four months later, the patient reported no recurrence of headache and vomiting. A neuroophthalmological examination showed no visual field loss or papilledema has also regressed.

CASE 3

A 9 -year-old boy had initially blurred vision (described as sparkling: many moving black points),

pain in his left eye that was associated with visual loss for a few hours which have occurred four or five times so far at presentation. In December 2007, the patient was referred to an other hospital with these symptoms. At that time neuroophtalmological examination revealed bilateral optic disc edema and no focal neurologic signs. An MRI scan of brain revealed bilateral diffuse optic neuritis. Cranial magnetic resonance anjiography was normal. He was treated with intravenous methyl prednisolone pulse 1 g daily for three days for optic neuritis. The family history was positive for protein C deficiency, Factor V Leiden mutation (father), protein C deficiency (sister).

The patient presented to our hospital for the first time in February 2008 with recurrence of visual impairment, headache and tiredness. On admission the patient was irritable and had bilateral optic disc edema and no focal neurologic signs. The CSF opening pressure was 30 cmH_20, and analysis of the fluid gave normal results. Angiography of the bilateral carotid and left vertebral arteries showed poor filling of most of the superior sagittal sinus and a filling defect in the left proximal transverse sinus. The extensive thrombosis was then visualized by MRI. A search for an underlying coagulopathy revealed: the prothrombin time was 10.6 (normally 10.2 to 12.2) seconds, the partial thromboplastin time 24.7 (normally 24.0 to 33.4) seconds and the platelet count 400 (normally 150 to 350) x 109/L. The plasma concentration of protein C was 73% (70-100%), protein S (total) 90% (90-130%), lipoprotein a 23 mg/dL (0-30 mg/dL) and homocystein 3.8 mmol/L (0-12 mmol/L), Factor VIII 143% (50-150%), Factor IX 143% (50-159%), Factor XI 112% (50-150%), Factor II 141%(50-15-), Factor V 147%(50-150%), Factor VII 125% (50-150%), Factor XII 103% (50-150%). No anticardiolipin antibody was found, and the plasma antithrombin III level was 110 (70-125%) U/mL. There was no clinical evidence to suggest lupus, and the antinuclear antibody titre was negative. Heterozygote state of the factor V Leiden mutation and a homozygote state of the MTHFR mutation was found. Low-molecular-weight heparin was given to him subcutaneously (1 mg/kg/day) for three months.

In March 2008, headache, blurred vision recurred. He noted recurrent nausea and he experienced permanent emesis for one week. Topiramate was initiated and gradually reached to a given at a dose of 200 mg/day. He became asymptomatic over the four months, and the papilledema resolved.

DISCUSSION

We report our experience with topiramate, a broad spectrum antiepileptic drug, for the treatment of pediatric IIH; one obese adolescent girl, one resistant to conventional therapy and one with superior sagital sinus thrombosis. All of them showed a marked improvement.

Although a number of treatments have been advocated for IIH, currently there is no evidence-based management strategy in children.[5] Treatment of underlying predisposing condition and/or withdrawal of the precipitating factor may result in the resolution of clinical symptoms. Many anectodal reports have suggested that weight loss for obesity may be effective in treating adulthood IIH. Complete resolution of IIH has been reported following the withdrawal of the precipitating agent such as tetracyline or minocycline.

Invasive interventions such as serial LPs and surgery are considered if visual loss is severe, progressive, or not responding to medicines. Repeat LPs might provide only temporary symptom relief and are traumatizing to the patient and the parents.[6,7]

Acetazolamide is the the most commonly used first-line medical approach in with IIH.[6,8-10] It is a strong carbonic anhydrase inhibitor. It acts by inhibition of CSF secretion or production by the choroid plexus. The inhibition of carbonic anhydrase could cause a reduction of sodium ion transport across choroid plexus epithelium. It can also act on the proximal renal tubule and induce a weak alkaline diuresis. Furosemide or corticosteroids can be used as an adjunct or a second line medical therapy for those who do not respond to acetozolamide treatment.

Topiramate is a sulfamate-substituted monosaccharide that has been found effective in headache from increased CSF pressure and has been

previously reported in incapacitating headache from idiopathic intracranial hypertension in adults.[4,11,12] Inhibitory effect on carbonic anhydrase isoenzymes is the rationale for using this anticonvulsant in intracranial hypertension. Reduction of intracranial CSF pressure by topiramate is attributable to the inhibition of carbo-anhydrase II and IV isoenzymes, and thus reduction of CSF production.[13] It is likely to inhibit these isoenzymes in erythrocytes and possibly in other tissues. The concentration in the brain parenchyma in humans has not been determined, but based on the studies in rats, parenchymal steadystate concentrations is thought to be about one third that of plasma.[13] Therefore, it is thought that isoenzymes II and IV may be inhibited appreciably within the brain of patients receiving high doses of topiramate. Topiramate has also been shown to cause dose-dependent weight loss in patients being treated for epilepsy, affective disorders and for migraine prophylaxis in several studies.[14] The mode of action of topiramate in migraine prophylaxis is not certain, but topiramate is reported to modify several receptor-gated and voltage-sensitive ion channels, including voltage-activated Na^{+2} and Ca^{+2} channels and non-*N*-methyl-[scap]d[r]- aspartate receptors. These mechanisms of actions and enhancement of gama-aminobutyric acid-mediated neurotransmission might have a role in prevention of migraine.[15] Weight loss was as result of loss of appetite associated with its effect on energy metabolism.[14] The combination of carbonic anhydrase inhibition reducing CSF production and appetite suppression which causes weight loss is the indication for the use of topiramate in the treatment of IIH. Overall, there is only one report on the use of topiramate for pediatic IIH.[4] This case report suggested potential benefit for a teenage boy with Behçet's disease.

Our first patient is an obese adolescent girl (body mass index 33.1) with severely symptomatic IIH who had incapacitating headaches and elevated intracranial pressure (opening pressure on lumbar puncture of 28 cmH_2O). We initiated topiramate for the treatment of IIH. After six months all clinical signs and symptoms completely resolved. Although we are aware that acetozolamide should be the first line drug for this patient, we decided to give her topiramate due to her obesity and headaches.

The second case was treated with acetozolamide and serial LP's. Ineffectiveness and refusal of these measures necessitated application of other treatment options for headache and visual loss. We then treated him with topiramate for IIH. He gave excellent response to topiramate demonstrating that topiramate may be effective in patients with IIH who have failed to respond to acetozolamide or recurrent LP's.

Cerebral venous sinus thrombosis is a rare cause of idiopathic intracranial hypertension. IIH is thought to derive from increased CSF production or decreased CSF absorption (absorptive block), either from increased pressure in the dural venous sinuses or lesions of the arachnoidal villi. Once the intracranial pressure raises above a certain level, pressure in the superior sagittal sinus increases due to collapse of the transverse sinuses.[16] The heterozygote Factor V Leiden and homozygote MTHFR mutation were detected during diagnostic workup of a questionable hypercoagulability in the third patient. No mutations in the Factor V or prothrombin genes were detected. The treatment of patients with IIH in cerebral venous thrombosis is controversial. Some authors suggesting measures for anticoagulation or thrombolysis and others advocating supportive therapy only. We treated our patient with topiramate which has just been used in one patient before.[17] Over time there was marked resolution of the extensive thrombosis.

As demonstrated in our patients, and concurring with the recent experience of others, topiramate may also be beneficial in the treatment of childhood IIH. This report may serve as a reminder that topiramate may be the first line drug in obese adolescents patients and sinus thrombosis with IIH, and also may serve as an alternative therapuetic option in failure to respond to acetozolamide or recurrent LP's. Thus, more controlled trials should be carried out to explore the efficacy of topiramate in children with IIH.

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