West syndrome, can topiramate be on top?

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ABSTRACT

الأهداف: تحديد فعالية التوبايراميت (Topiramate) في علاج التشنجات التي تصيب الأطفال (متلازمة وست) والنوبات اللاحقة وما إذا كان هناك تحسن في نتائج تخطيط الدماغ الكهربائي.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في قسم الأطفال بمستشفى الملك فهد الجامعي، جامعة الدمام، الدمام، المملكة العربية السعودية وذلك خلال الفترة من يناير 2004م إلى ديسمبر 2008م. وشملت هذه الدراسة 18 مريضاً مصاباً بمتلازمة وست (7 ذكور و11 أنثى) وتتراوح أعمارهم ما بين 2–14 شهراً. ولقد تم إعطاء المرضى عقار التوبايراميت بجرعة لا تتجاوز 12 ملغ لكل كيلوغرام مرة واحدة يومياً.

النتائج: أشارت النتائج إلى أن مسببات المرض كانت مجهولة المنشأ في 9 مرضى (50%)، ومصحوبة بأعراض في 6 مرضى (33%)، ومجهولة السبب في 3 مرضى (17%). وبعد العلاج بالتوبايراميت اختفت التشنجات لدى 6 مرضى (33%)، فيما تحسنت هذه التشنجات بنسبة تزيد عن 50% لدى 8 مرضى (44%)، ولم يكن هناك تغير في التشنجات لدى مريضين (11%)، وساءت التشنجات عند مريض واحد (6%). لقد عانى 8 مرضى من التشنجات اللاحقة غير أنه بعد العلاج بعقار التوبايراميت اختفت هذه التشنجات في مريضين (25%)، وتحسنت بنسبة تزيد عن 50% في مريضين (25%)، ولم تتغير التشنجات في 4 مرضى (50%). لقد أظهر تخطيط الدماغ الكهربائي نمط اضطراب النظم المترافع في 14 مرضى (78%) وذلك قبل استخدام العلاج، فيما كانت نتائج تخطيط الدماغ الكهربائي بعد استخدام التوبايراميت طبيعية في مريض واحد (5%)، وتحسنت في 3 مرضى (17%)، ولم تتغير نتائج التخطيط في 8 مرضى (44%)، بينما تغير التخطيط إلى أنماط أخرى في 3 مرضى (17%). لقد أصيب 3 من المرضى بتأثيرات جانبية إثر تناول العقار مثل نقص في الوزن وتهيج مما أدى إلى وقف العلاج عن مريضين.

خاتمة: أثبتت الدراسة مدى فعالية عقار التوبايراميت في التخلص من أعراض متلازمة وست، غير أنه لم يكن له تأثير ملحوظ على نتائج تخطيط الدماغ الكهربائي. ولقد كان العلاج مُحتمل من قبل المرضى مع تأثيرات جانبية قليلة جداً.

Objectives: To determine Topiramate efficacy on treatment of infantile spasms and ancillary seizures, and whether there were any improvements on EEG.

Methods: A retrospective study of 18 patients with infantile spasms recruited from the Pediatric Unit at King Fahd Hospital of the University, Dammam University, Saudi Arabia was carried out between January 2004 and December 2008. Topiramate was used as treatment in 7 males and 11 females aged 2-14 months. The maximum dose was 12 mg/kg/day.

Results: The etiology in 9 (50%) patients was cryptogenic, 6 (33%) symptomatic, and 3 (17%) idiopathic. After Topiramate treatment 6 (33%) were spasm free, 8 (44%) had ≥50% reduction, 2 (11%) had no change, and one (6%) had worsening of their spasms. Eight patients had ancillary seizures, 2 (25%) were seizure free, 2 (25%) had ≥50% seizure reduction, and 4 (50%) had no change in the ancillary seizure. The EEG showed hypsarrhythmia in 14 (78%). Post Topiramate, the EEG was normal in one (5%), improved in 3 (17%), showed persistent hypsarrhythmia in 8 (44%), and evolved to other features in 3 (17%). Three patients developed side effects such as weight loss and irritability, for which 2 patients stopped the medication.

Conclusion: Topiramate has a good effect on the clinical features of West syndrome, but not on the EEG. It was tolerated with minimal side effects.

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West syndrome is one of the severe and refractory epilepsy syndromes characterized by a triad of spasms that usually occur in clusters, developmental delay, and diffuse and profound paroxysmal EEG

abnormalities known as hypsarrhythmia associated with psychomotor regression.[1] It is a severe form of epilepsy that can evolve into Lennox-Gastaut and other severe forms of epilepsy associated with severe neuro disability. Although adrenocorticotropic hormone (ACTH), prednisolone, vigabatrin, and others can ameliorate or treat the spasms in certain cases depending on the etiology, their side effects render them more and more unsuitable as first line, and some are unlicensed to be used in children in some countries. Topiramate is one of the new generations of antiepileptic drugs (AEDs) that have been shown to be effective in the treatment of the spasms that constitute the major clinical presentation of this syndrome.[2] The spasms are notoriously resistant to single and multiple AEDs and are associated with poor long term outcome.[3] Both ACTH and vigabatrin were shown to be effective in previous studies, however, ACTH causes weight gain and blood pressure elevation, among other side effects,[4] and vigabatrin causes a bilateral concentric constriction of peripheral visual fields in 30-50% of patients exposed to it for several years, and it is asymptomatic and requires regular surveillance on the part of the patient.[5] Topiramate is one of the novel new generation AEDs and is a sodium channel blocker and has been shown to be effective in spasm control at reasonable doses. Therefore, the objective was to investigate the clinical effect of Topiramate on infantile spasms in our population, and to determine what effects it has on ancillary seizures in our patients, and the electrographic effect on EEGs in the specified population.

Methods. A retrospective study was performed examining case notes of patients managed in King Fahd Hospital of the University, Dammam, Kingdom of Saudi Arabia between January 2004 and December 2008 presenting with the clinical picture of infantile spasms. Patients were either started on Topiramate de novo or it was added as adjunctive therapy to other AEDs, which have failed to control the spasms. Patients had to have features consistent with infantile spasms (for example hypsarrhythmia, modified hypsarrhythmia, or electro decremental electrographic seizures associated with a recognizable clinical infantile spasm). Patients were excluded from the study if they had a recent history or evidence of other significant medical disease, or CT or MRI evidence of a progressive neurologic lesion. Patients were monitored for side effects by verbal interrogation, blood tests, and ultrasound of the abdomen as the dose was slowly titrated to achieve clinical response. An EEG was carried out prior to and after Topiramate therapy, and ancillary seizures were monitored. All case notes were revised by the authors including hospital management, and outpatient reviews, and all data was entered into a data sheet and was analyzed and results were revised.

Statistical analysis was carried out using Microsoft Excel 2003. The results are presented as absolute numbers, percentages, median, range, and mean +/- SD.

Table 1 - Spasms and ancillary seizures.

Characteristics	n (%)
Seizure frequency, mean (range), total of 17	
Spasms/day	11.6 (2-50)
Ancillary seizures/day	12.5 (3-20)
Response to Topiramate	
Spasm free	6 (33)
≥50% spasm reduction	8 (44)
No change in spasms	2 (11)
Worsening of spasms	1 (6)
Lost to follow up	1 (6)
Number of patients with ancillary seizures	8
Ancillary seizure frequency/dat, mean (range)	12.5 (3-20)
Seizure free post topiramate	2 (25)
>50% seizure reduction	2 (25)
No change in ancillary seizures	4 (50)

Table 2 - The EEG findings before and after Topiramate treatment.

Findings	n (%)
EEG prior to Topiramate	
Hypsarrhythmia	14 (78)
Normal	nil
Other features	4 (22)
EEG post Topiramate	
Hypsarrhythmia	8 (44)
Normal	1 (5)
Improved	3 (17)
Lost to follow up	3 (17)
Others	3 (17)

Results. The study included 18 patients, 7 (39%) males and 11 (61%) females with a mean of age of 7.6 months, ranging between 2-14 months, and weight of 8.52±2.8 Kg. The etiology was cryptogenic in 9 (50%), symptomatic in 6 (33%), and idiopathic in 3 (17%). The median age at spasm onset was 5.7 months and the duration of spasms prior to Topiramate was 10.9 months (median), with a range of 2 days to 31 months. The number of children on concomitant AEDs was 8 (44%) children on ≥2 AEDs, and 6 (33%) on one drug, and only 4 (23%) on Topiramate monotherapy. The mean ± standard deviation of number of previous AEDs was 1.7±1.4. **Table 1** details the number of spasms and ancillary seizures. The mean ± SD dose of Topiramate was 11.7±5.8 mg/kg, with a median (range) of 12mg/kg (5.1-26). Only 3 (17%) patients developed side effects

in the form of irritability, weight loss, and fever, with only 2 (11%) patients in total discontinuing treatment due to side effects. The duration of Topiramate use until the end of the study ranged between 2 weeks to 48 months. **Table 2** details the EEG findings before and after Topiramate treatment.

Discussion. The study revealed a prevalence of females with a total of 11 compared with 7 males, which is interesting as infantile spasms usually have a male preponderance.[1] The age varied between 2-14 months, with a mean of 6.7 months. The fact that infantile spasms can occur beyond the first year of life needs to be stressed. West syndrome usually presents between 4 and 6 months, and before 12 months in 90% of cases. The neurological development in this group was as follows:- Neurological development as per chronological age at presentation was normal in one (6%), and abnormal in 17 (94%). Neurological examination at presentation was normal in one and abnormal in 17 patients. Therefore, there was an obvious delay in attaining milestones appropriate for age, and also they failed their neurological examination at the first visit. As for the etiology, the patients in this group were thoroughly investigated with radiological, hematological, and other investigations looking for a possible cause and the symptomatic cases comprised neurocutaneous syndromes in 2 patients, hypoxic ischemic encephalopathy in 2 patients, Aicardi syndrome in one patient, and non-ketotic hyperglycinemia in one patient. Half the patients were cryptogenic, and only 3 were idiopathic. Infantile spasms studied by Glauser et al[3] revealed that out of 11 patients only 2 were cryptogenic and 9 were symptomatic. As more and more genetic tests and extensive metabolic and mitochondrial tests become available, the cryptogenic group will become less at the expense of a widening symptomatic group. There are different causes for infantile spasms including prenatal, perinatal, and postnatal factors. Infection (CMV fetopathy), ischemia (preterm or term), postnatal ischemia (near miss), various brain dysgenesis disorders (lissencephaly, megalencephaly), chromosomal causes (Down's, del 1p36) or single gene disorders such as ARX mutations and STK9 mutations, neurocutaneous diseases, and inborn errors of metabolism are all known amongst other disorders to present as infantile spasms. The list is exhaustive and our patients underwent all investigations looking for a cause, except for the gene mutations, as we do not have these facilities in our hospital.

The spasms in this group were quite refractory with a median of spasms prior to Topiramate of 10.9 months, and 14 patients were already on some form of antiepileptic treatment. Six patients were spasm free on Topiramate, and 8 had a reasonable drop in their spasm frequency on Topiramate. As far as the ancillary seizures are concerned, only 25% of the patients were free and another 25% had a considerable drop in their seizure frequency at the end of the study. Fifty percent, however, had no change in the ancillary seizure record. The latter were 4 patients with aggressive and frequent types of seizures. One had non-ketotic hyperglycinemia with severe uncontrolled seizures and another had drop attacks, the third had at least 6 types of seizures occurring very frequently and the last one had generalized tonic clonic seizures as well as focal seizures. As for the dose of Topiramate, it was very reasonable at a median of 12mg/kg, as compared with other studies (maximum 50mg/kg/d).[3] Topiramate is a broad spectrum novel AED, that has been shown in subset analysis to be effective and well tolerated as a monotherapy in children and adolescents even at higher doses titrated to 400 mg/day.[5,6] Topiramate levels were not checked in this series, but the dose was titrated to maximally control spasms. The acid base profile, weight, and renal function were all monitored as those children were followed up. Side effects were minimal being reported only by 3 patients, and only 2 (11%) stopped the medication. This actually matches literature studies in that side effects are usually somnolence and decreased appetite, which may even resolve spontaneously, or if not by cessation of therapy.[7] In our study, weight loss and worsening seizures were the reason to stop Topiramate. In a study published by Al-Ajlouni et al,[7] 13% had to stop treatment because of the above 2 side effects. The patients in this study continued to tolerate Topiramate probably due to slow titration. By the end of the study, 6 of the patients continued on Topiramate for more than 3 years either due to ancillary seizures or evolution of the spasms to Lennox-Gastaut. Lastly, on the EEG, 78% had hypsarrhythmia prior to Topiramate and this persisted from 6 months up to a year post Topiramate in 44%. Only 5% had a normal EEG and 17% improved post topiramate.

The limitations of this study were mainly related to the number of cases, as the University Hospital is not accessible to all different nationalities resident in Saudi Arabia. This study needs to be repeated in a public hospital and the varied etiology and response to treatment can be further assessed. Also the lack of follow up in some of the patients in view of population movement, and so forth, makes follow up EEGs a challenge to document as patients may be followed up in other easily accessible hospitals, especially if they are not nationals.

In conclusion, Topiramate at a median dose of 12 mg/kg was effective in reducing clinical spasm frequency as well as ancillary seizures frequency with

good tolerability and minimal side effects with a minor effect on the EEG. There is a great need for prospective studies to monitor long-term effects, especially on the cognitive and neuropsychiatric status of those children as they outlive the infantile spasms and proceed to develop other forms of childhood epilepsy.

References

1. Dulac O, Ballaban-Gil KR, Moshe SL. West syndrome [Internet]. Connecticut: ILAE 2005 [updated 2003 August 24; cited 2010 November] Available from URL: http://www.ilae-epilepsy.org/ctf/west_syndrome.html
2. Hsieh MY, Lin KL, Wang HS, Chou ML, Hung PC, Chang MY. Low dose topiramate is effective in the treatment of infantile spasms. ***Chang Gung Med J*** 2006; 3: 291-296.
3. Glauser TA, Clark PO, McGee K. Long-term response to topiramate in patients with West syndrome. ***Epilepsia*** 2000; 41(Suppl 1): 91-94.
4. Partikian A, Mitchell WG. Major adverse events associated with treatment of infantile spasms. ***J Child Neurol*** 2007; 12: 1360-1366.
5. Wheless JW, Ramsay RE, Collins SD. Vigabatrin. ***Neurotherapeutics*** 2007; 4: 163-172.
6. Ben-Menachem E. Is topiramate tops? ***Epilepsy Curr*** 2008; 3: 60-61.
7. Al Ajlouni S, Shorman A, Daoud AS. The efficacy and side effects of topiramate on refractory epilepsy in infants and young children: a multi-center clinical trial. ***Seizure*** 2005; 14: 459-463.

Related topics

Unalp A, Uran N, Hizli T, Ozturk A. Topiramate as a long-term therapy in children with refractory epilepsy. ***Neurosciences (Riyadh)*** 2008; 13: 391-394.

Hassan AA, Jan MM, Shaabat AO. Topiramate for the treatment of intractable childhood epilepsy. ***Neurosciences (Riyadh)*** 2003; 8: 233-236.

Jan MM, Baeesa SS, Shivji ZM. Topiramate for the treatment of infants with early myoclonic encephalopathy. ***Neurosciences (Riyadh)*** 2003; 8: 110-112.