

# Brief Communication

## Treatment of infantile spasms in Saudi Arabia

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### ABSTRACT

**Objectives:** To evaluate the treatment approach and compliance of pediatric neurologists with evidence-based guidelines across Kingdom of Saudi Arabia (KSA). These guidelines that clarify the optimal management of infantile spasms (IS) are not widely followed for various practical reasons.

**Methods:** Physicians practicing in the field of pediatric neurology in KSA were contacted from the database of national societies. A cross-sectional study was conducted using a structured 20-item on-line survey designed to examine their clinical experience with IS and their treatment choices.

**Results:** A total of 52 pediatric neurologists completed the survey (69% estimated capture rate). They received their formal training within KSA (40%), North America (33%), or Europe (14%). The majority practiced in 2 major cities, Riyadh (46%) or Jeddah (19%). Vigabatrin was favored over adrenocorticotropic hormone (ACTH) as first line drug for patients without tuberous sclerosis complex (48% vs. 21%). Several factors correlated with correctly selecting ACTH as first line including western training (33% vs. 5%,  $p=0.001$ ), practicing in the city of Riyadh (25% vs. 14%,  $p=0.001$ ), or having >10 years of clinical experience (25% vs. 5%,  $p=0.017$ ). Reasons for not complying with the recommended treatment guidelines included lack of availability of ACTH (42%), side effect profile of steroids (29%), and personal preferences (14%). Only 4% admitted lack of awareness of the currently published management guidelines.

**Conclusion:** Many pediatric neurologists in KSA are not following the published IS management guidelines. Using ACTH as first line correlated with their training, practice location, and years of experience. Lack of drug availability and side effect

profile were common reasons for not complying with the management guidelines.

*Neurosciences 2018; Vol. 23 (3): 258-261*  
doi: 10.17712/nsj.2018.3.20180015

Infantile spasms (IS) represent a severe epilepsy syndrome that require prompt diagnosis and treatment.<sup>1</sup> Such early management could favorably influence the ultimate seizure control and long-term developmental outcome.<sup>2</sup> The majority of infants (70%) are grouped into a symptomatic group with an identifiable underlying etiology, most importantly tuberous sclerosis complex.<sup>1,2</sup> In addition to identifying such etiologies and early treatment, factors that can influence the prognosis include the utilized treatment protocols.<sup>3</sup> Steroids, specifically adrenocorticotropic hormone (ACTH) and oral prednisone, were found to be the most effective initial treatment, excluding patients with tuberous sclerosis complex where Vigabatrin (VGB) was found to be the preferred initial drug.<sup>4</sup> Other available drugs include, topiramate, levetiracetam, valproic acid, benzodiazepines, lamotrigine, sulthiame, pyridoxine (in selected patients), and zonisamide, all can be used with variable success. Non-pharmacological treatments should also be considered in selected resistant cases and include the ketogenic diet, intravenous immunoglobulin (IVIG), and epilepsy surgery.<sup>4</sup> Evidence-based guidelines regarding the optimal management of IS that have been published are mostly based on personal preference and individual expert opinions rather than clear clinical evidence.<sup>5</sup> Therefore, the approaches to IS treatment remain influenced by a myriad of factors, including the availability of medications, side effects profiles, cost, personal preferences, and experiences of the treating physicians. In this study, we aim to evaluate the treatment approaches across Kingdom of Saudi Arabia (KSA) and examine the compliance of pediatric neurologists with the current IS management guidelines and the obstacles to its application.

**Methods.** A list of pediatric neurologists was obtained from the membership database of the Saudi Pediatric Neurology Society and Saudi Epilepsy Society. The authors are also personally aware of physicians practicing in the field through activities of these societies, in addition to involvement in the pediatric neurology training programs and neuroscience conferences across KSA. Further contact details of practicing pediatric neurologists were obtained from a national “neuroscience forum”, which is a smart phone application that involves most practicing neuroscientists.<sup>6</sup>

**Disclosure.** The authors have no conflict of interests, and the work was not supported or funded by any drug company.

A structured 20-item questionnaire designed to examine the treatment choices for patients with IS was electronically mailed to all identified pediatric neurologists across Saudi Arabia during the months of May-June, 2017. Two reminders were sent to their smart phones using the "neuroscience forum" database. Key questions included details of their demographics, training, experience, and practice. Specific questions and choice of drugs were requested using different case scenarios and lists. We also enquired about the number of infantile spasm patients they see per year and their preferred treatment protocol. A final open-ended question was included to further understand the limitations in adhering to the recommended treatment guidelines and to provide any additional comments or suggestions. King Abdulaziz University Hospital's ethics committee approved the study design and questionnaire. Informed consent was obtained during the voluntary participation in the study.

Data was tabulated in Excel sheets and statistical analysis was performed using SPSS 21 (IBM Corp., Armonk, NY, USA). Descriptive analyses were performed and the variables were examined using chi-square test. A *p*-value of 0.05 or less was considered significant.

**Results.** A total of 52 pediatric neurologists practicing within KSA completed the survey. Most of the respondents were male (65.5%) with variable age distribution of <35 years in 15.5%, 35-45 years in 36.5%, 45-55 years in 33%, and >55 years in 15%. The majority received their formal pediatric neurology training within Saudi Arabia (40%), North America (33%), or Europe (14%). They practiced within various regions of the country; however, 65% of them worked in 2 major cities, the capital city of Riyadh (46%) or Jeddah (19%). All participating neurologists were hospital-based, most commonly (48%) within institutions belonging to the Ministry of Health. The remainder were distributed between university hospitals (19%), military medical facilities (25%), or private institutions (8%). Their years of experience ranged from <5 years in 21%, 5-10 years in 21%, 10-20 years in 38.5%, and more than 20 years of experience in 19.5%.

All included pediatric neurologists stated that they commonly evaluate and follow patients with IS ranging in number from less than 10 cases per year in 54%, 10-20 in 29%, and more than 20 cases per year in 17%. Those practicing in the city of Riyadh were more likely to evaluate >20 cases of IS per year when compared

to other regions (24% vs. 11%, *p*=0.029). Table 1 summarizes their first and second line antiepileptic drug choices for treating their patients with IS excluding those caused by tuberous sclerosis complex. Vigabatrin was generally favored over steroids (Table 1). Several factors correlated with correctly selecting ACTH as the first drug of choice including having western training (33% vs. 5%, *p*=0.001), practicing in the city of Riyadh (25% vs. 14%, *p*= 0.001), and having more than 10 years of clinical experience (25% vs. 5%, *p*=0.017). Other factors including age, gender, or hospital setting had no significant correlations. Reasons for not complying with the recommended treatment guidelines included lack of availability of ACTH in 42%, side effect profile of steroids in 29%, and personal preferences in 14%. Only 4% of the participating pediatric neurologists admitted lack of awareness of the currently published treatment guidelines. For the treatment of IS caused by tuberous sclerosis complex, most pediatric neurologists (92%) correctly selected vigabatrin. Table 2 summarizes the antiepileptic drug (AED) choices for resistant cases that failed first and second line treatments. Topiramate,

**Table 1** - First and second line AED choices for treating patients with infantile spasms excluding those caused by tuberous sclerosis complex. N=52

AED	First line		Second line	
	n	(%)	AED	n (%)
Vigabatrin	25	(48)	Vigabatrin	19 (36.5)
<i>Steroids</i>	22	(42)	<i>Steroids</i>	24 (46)
ACTH	11	(21)	ACTH	9 (17)
Oral	11	(21)	Oral	15 (29)
Valproic acid	4	(8)	Topiramate	5 (9.5)
Other	1	(2)	Other	4 (8)

AED - antiepileptic drug, ACTH - adrenocorticotropic hormone

**Table 2** - Treatment choices for resistant cases that failed first and second line AEDs.

Treatment	n	(%)
Topiramate	39	(75)
Pyridoxine	37	(71)
Levetiracetam	36	(69)
Valproic acid	26	(50)
Clonazepam	22	(42)
Oral steroids	19	(36)
Ketogenic diet	19	(36)
Vigabatrin	13	(25)
ACTH	12	(23)
IVIG	5	(10)

ACTH - adrenocorticotropic hormone, IVIG - intravenous immunoglobulin

pyridoxine, and levetiracetam were the most common choices (Table 2). Although most pediatric neurologists (71%) recognize epilepsy surgery as an option in selected patients, they rarely referred their resistant cases for surgical evaluation.

**Discussion.** Our study confirms that many pediatric neurologists in Saudi Arabia are not following the published IS management guidelines. Over adrenocorticotrophic hormone is considered the first effective treatment choice for IS and in resolution of hypsarrhythmia based on level B evidence.<sup>5</sup> Only 21% of the included pediatric neurologists used ACTH as first line despite many of them practicing in the capital city of Riyadh, which has the major tertiary care institutions with experienced western trained pediatric neurologists who evaluated larger volumes of infantile spasm patients as compared to other regions of the country. Pediatric neurologists practicing in this region were more likely to use ACTH as first line. As well, those who received western training (North America or Europe) were more likely to use ACTH as compared with Saudi trained pediatric neurologists suggesting heightened exposure and experience with such treatment during their training. Finally, pediatric neurologists with more than 10 years of clinical experience were more likely to select ACTH as first choice reflecting its heightened efficacy that is confirmed by their longer practice and experience.

A major factor for not selecting ACTH as first choice was lack of availability, which may also explain the regional differences in its use as smaller and more peripheral centers may have had more limitations in its availability as compared to larger tertiary care institutions. This may also explain the significant percentage of neurologists who used other form of steroids as first line instead of ACTH. In addition, side effect profile of steroids remained a concern for many pediatric neurologists contributing significantly to limited ACTH use. On the other hand, vigabatrin was more commonly used despite of its side effect profile. A more recent report by a European interdisciplinary guideline committee expanded the first line drugs to include ACTH, other corticosteroids, and vigabatrin.<sup>7</sup> Although most pediatric neurologists (71%) recognize epilepsy surgery as an option in selected patients, they rarely referred their resistant cases for surgical evaluation. However, many pediatric neurologists considered vitamin B6 and the ketogenic diet for resistant cases which is consistent with the recent literature.<sup>8,9</sup>

There are some limitations to our study. It is possible that we were unable to capture the opinion of all pediatric neurologists across the country. A total of 52 pediatric neurologists practicing within KSA completed the survey. A recent Saudi study estimated a total number of 75 pediatric neurologists across the country giving us a 69% capture rate.<sup>10</sup> In addition, the presented data is based on the perceived opinions and experiences of the respondents and may be exaggerated or may not accurately reflect their actual practice. A Further study examining the actual practice is needed.

We conclude that many pediatric neurologists in Saudi Arabia are not following the published IS management guidelines. Using ACTH as first line correlated with their training, practice location, and years of experience. Lack of drug availability and side effect profile were common reasons for not complying with the management guidelines. Our findings highlight the need for improving the availability of ACTH across the country and improving the knowledge and experience of IS management of practicing pediatric neurologists, particularly those working outside major tertiary care centers.

Received 11th January 2018. Accepted 11th April 2018.

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