



Sibling response to initial antiepileptic medication predicts treatment success



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ABSTRACT

Objective: A recent study focusing on a response to antiepileptic drugs (AED) among siblings for epilepsy showed a similar response among epileptic siblings to specific AEDs or AED combinations. Currently, however, family history of treatment response to AEDs is not readily employed in deciding which initial medication to use when treating patients with epilepsy. We tested the hypothesis that sibling response to initial AED predicts treatment success.

Methods: Presumed siblings were identified from a single-center database of patients diagnosed with epilepsy by matching last name, address, and name of parent(s). We identified 28 sibling pairs and two sibling trios with epilepsy. Seventeen of these sibling pairs were started on the same initial AED, with 15 sibling pairs having the same type of epilepsy. The remaining 11 pairs were started on a different initial AED, with 8 of these sibling pairs having the same type of epilepsy. Subjects with seizure freedom for a period of ≥ 1 year were classified as a “responder”.

Results: When at least one of the sibling pair responded to an initial AED, the proportion of the other siblings also responding to the initial AED was significantly higher if the siblings were treated with the same AED (8/11) compared to siblings who were treated with different AED (1/10) (Fisher's exact test, p-value = 0.0075).

Significance: These findings suggest that sibling response to initial AED is predictive of the success of AED therapy. This study is limited by a small cohort and retrospective design. Future, larger prospective studies are needed to reproduce and further validate these findings.

1. Introduction

Antiepileptic drugs (AEDs) are the first line of treatment for epilepsy, but contain several disadvantages such as unpredictable efficacy, medication compliance issues, drug interaction, and adverse drug effects. Clinicians are always careful in selecting AEDs and aim to obtain seizure-freedom without such disadvantages. The selection of AEDs depend on an individual physician's judgment based on type of epilepsy, patient characteristics, experiences and physician preferences (Azar and Abou-Khalil, 2008). A recent study focusing on a response to AEDs among siblings for epilepsy showed a similar response among

epileptic siblings to specific AEDs or AED combinations (Sonmezturk et al., 2012).

The determinants of variable drug response in individuals with epilepsy are not well understood. However, interindividual variability in efficacy may be related to type and pathophysiology of epilepsy, comorbid factors, genetic factors such as polymorphisms in genes encoding drug-metabolizing enzymes, transporters, or drug targets or environmental factors such as diet, sleep, and compliance. The relative contributions of genetic and environmental factors in AED efficacy are not well understood. Therefore, an understanding of the role of genetic factors in AED efficacy is essential in a clinical setting. Our experience

Abbreviation: AEDs, antiepileptic drugs

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in our institution suggests that family history of treatment response to AEDs is not readily employed in deciding which AED to use when treating patients with epilepsy. A guideline on selecting of an AED by the International League Against Epilepsy (ILAE) in 2006 has listed multiple variables to be considered but treatment response to AED in family members is not included (Glauser et al., 2006). We hypothesized that sibling response to initial AED predicts treatment success in the other sibling. The present study focused on whether AEDs effective for one sibling, would also be effective for the other siblings as an initial epilepsy treatment.

2. Methods

We conducted a retrospective chart review from a single-center neurology clinic database at Children's Hospital of Michigan. The chart review was covered from 2008 to 2017. Some of the patients that were referred to our neurology clinic had already been started on AEDs. Siblings who have epilepsy were identified based on the same family (last) name, home address, home phone number and parent(s) name listed in the electronic medical records. The extracted data include the age of epilepsy diagnosis, gender, epilepsy classification, diagnostic tests including neuroimaging and EEG, response or nonresponse to treatment, reasons for the discontinuation of initial AEDs or addition of other AEDs, and names of initial AEDs given. Epilepsy was classified into generalized and focal epilepsy based on classification by the ILAE (Hirsch et al., 2016; Scheffer et al., 2016). The patients were treated by ten different board certified child neurologists at Children's Hospital of Michigan. Response to treatment was considered epilepsy remission, defined as seizure freedom for a period of ≥ 1 year. Nonresponse was considered anything other than epilepsy remission. The dose of initial AEDs was increased until patients obtained a seizure-free period. When patients continued to have seizures on an adequate dose of initial AEDs or developed adverse events, other AEDs were added to the treatment. We utilized Fisher's exact test to compare the response to initial AEDs between the sibling pairs treated with the same initial AEDs, and those treated with different initial AEDs. This study was approved by the Human Investigation Committee of Wayne State University (IRB # 122808MP4E).

3. Results

We identified 62 epilepsy patients (39 boys, 63%) with 28 sibling pairs and two sibling trios. The age at epilepsy diagnosis ranged from 0 months to 16 years old (4.7 ± 3.3). Seventeen sibling pairs/trios were started on the same AED for initial treatment, with two of these sibling pairs having a different type of epilepsy, while the remaining 13 sibling pairs were started on a different initial AED, with three of these sibling pairs having a different type of epilepsy. There were 14 patients with generalized epilepsy, 45 patients with focal epilepsy, two patients with general/focal epilepsy, and one patient with infantile spasms. Among the same initial AED pairs/trios, 15 sibling pairs/trios have the same type of seizures. Among the different initial AED pairs, 10 sibling pairs have the same type of seizures (Tables 1 and 2). Overall, the most commonly used initial AED was oxcarbazepine ($n = 28$, 45%), followed by levetiracetam ($n = 12$, 19%), valproate ($n = 6$, 9.7%), ethosuximide ($n = 5$, 8.0%), topiramate ($n = 4$, 6.5%), phenobarbital ($n = 3$, 4.8%), carbamazepine ($n = 2$, 3.2%), vigabatrin ($n = 1$, 1.6%), and phenytoin ($n = 1$, 1.6%). In the same initial AED pairs/trios, oxcarbazepine was the most used AED ($n = 20$, 56%), followed by levetiracetam ($n = 8$, 22%). On the other hand, various AEDs were used in the different initial AED pairs: oxcarbazepine ($n = 8$, 31%), levetiracetam ($n = 4$, 15%), valproate ($n = 6$, 23%), phenobarbital ($n = 3$, 12%), topiramate ($n = 2$, 7.7%), ethosuximide ($n = 1$, 3.8%) and phenytoin ($n = 1$, 3.8%). Significantly different AEDs were used between the same initial AED pairs/trios and the different initial AED pairs (Fisher's exact test, p -value = 0.00065). The year of start of the initial AED

Table 1
Siblings pairs started on same initial medications.

Group number	Gender	Age of onset of seizure (years old)	The year of start of initial AED	Epilepsy classification	Initial medication	Response
4	M	7	2005	Focal	CBZ	R
	F	6 months	1989	Focal	CBZ	N
6	M	7	2004	Generalized	ESM	R
	M	4	2009	Generalized	ESM	R
10	F	18 months	2011	Generalized/focal	OXC	N
	F	7	2008	Focal	OXC	N
11	M	5	2011	Focal	OXC	R
	M	9	2015	Focal	OXC	R
14	F	4	2009	Generalized	OXC	R
	M	4	2005	Focal	OXC	R
15	M	8	2016	Focal	OXC	R
	F	8	2012	Focal	OXC	R
16	M	9	2013	Focal	OXC	R
	M	2	2007	Focal	OXC	R
18	F	4	2011	Focal	OXC	R
	M	14	2007	Focal	LEV	N
20	F	9	2006	Focal	LEV	N
	F	2	2014	Focal	LEV	N
21	F	2	2014	Focal	LEV	R
	M	0 months	2000	Focal	TPM	N
23	F	4	2002	Focal	TPM	N
	M	2	2009	Focal	LEV	N
24	F	2	2008	Focal	LEV	N
	M	16	2014	Focal	OXC	N
25	M	9	2002	Focal	OXC	R
	M	3	2014	Focal	LEV	R
27	M	15 months	2012	Focal	LEV	R
	F	4	2007	Focal	OXC	R
28	M	5	2007	Focal	OXC	R
	M	3	2009	Focal	OXC	R
28	M	5	2002	Generalized	ESM	N
	M	5	2002	Generalized	ESM	N
29	F	6	2010	Focal	OXC	R
	M	5	2006	Focal	OXC	R
30	M	4	2017	Focal	OXC	N
	M	2	2015	Focal	OXC	N

M, male; F, female; CBZ, carbamazepine; ESM, ethosuximide; OXC, oxcarbazepine; LEV, levetiracetam; TPM, topiramate; R, responder; N, nonresponder.

ranged from 1989 to 2017 in the same initial AED pairs/trios and from 1997 to 2014 in the different initial AED pairs (Tables 1 and 2).

3.1. Response to the initial AED

Overall, 52% (32/62) of patients became seizure-free with the initial AED. Out of a total 30 sibling pairs/trios, the clinicians chose the same AED for the second sibling in 17 instances as compared to a different AED in 13 instances as initial AED (p -value = 0.7961). Out of 17 pairs/trios siblings that received the same initial AED, there were eight pairs/trios where both siblings were responders, three pairs where only one sibling of the pair was a responder, and six pairs where both siblings were non-responders. Similarly, of the 13 sibling pairs, who received a different initial AED, there was only one pair with both siblings as responders, nine pairs where only one sibling was a responder, and three pairs with no responders.

The proportion of the other siblings also responding to the initial AED was significantly higher if the siblings were treated with the same medications (8/11) compared to siblings who were treated with different medications (1/10) (Fisher's exact test, p -value = 0.0075) (Fig. 1).

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