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High vigabatrin dosage is associated with lower risk of infantile spasms relapse among children with tuberous sclerosis complex

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ABSTRACT

After initially successful treatment of infantile spasms, the long-term cumulative risk of relapse approaches 50%, and there is no established protocol to mitigate this risk. Although vigabatrin may be an effective means to prevent relapse, there is little guidance as to ideal duration and dosage. Using a cohort of children with infantile spasms and tuberous sclerosis complex (TSC), we evaluated the potential association of post-response VGB treatment and the rate of infantile spasms relapse. Patients with infantile spasms and clinical response to vigabatrin were identified among a multicenter prospective observational cohort of children with TSC. For each patient we recorded dates of infantile spasms onset, response to vigabatrin, relapse (if any), and quantified duration and dosage of vigabatrin after response. Time to relapse as a function of vigabatrin exposure was evaluated using survival analyses. We identified 50 children who responded to VGB. During a median follow-up of 16.6 months (IQR 10.3–22.9), 12 (24%) patients subsequently relapsed after a median of 7.8 months (IQR 3.1–9.6). Relapse occurred after VGB discontinuation in four patients, and during continued VGB treatment in the remaining eight cases. In survival analyses, risk of relapse was unaffected by the presence or absence of VGB treatment (HR 0.31, 95%CI 0.01–28.4, $P = 0.61$), but weighted-average dosage was associated with marked reduction in relapse risk: Each 50 mg/kg/d increment in dosage was associated with 61% reduction in risk (HR

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0.39, 95%CI 0.17 – 0.90, $P = 0.026$). This study suggests that the risk of infantile spasms relapse in TSC may be reduced by high-dose vigabatrin treatment.

1. Introduction

Infantile spasms (IS) is the most common epilepsy syndrome with onset in the first year of life, affecting approximately 1 in 2500 infants (Shields, 2006). IS presents in a distinctive fashion with clusters of brief seizures called epileptic spasms (Fisher et al., 2017), and a spectrum of severe electroencephalographic abnormalities that include hypsarrhythmia (Hrachovy et al., 1984). Onset is often heralded by neurodevelopmental arrest or regression (Shields, 2006). Despite its relatively high incidence and this unique clinical presentation, diagnostic confusion and treatment delay are common and potentially devastating (Hussain et al., 2017a). Treatment delay is associated with reduced efficacy of first-line medications (O'Callaghan et al., 2017) as well as marked reductions in long-term neurodevelopmental outcomes. (O'Callaghan et al., 2011) First-line treatment options for IS include natural (Baram et al., 1996) and synthetic (Lux et al., 2004) adrenocorticotropic hormone (ACTH), prednisolone (Hussain et al., 2014) and vigabatrin (VGB) (Elterman et al., 2010). Although short-term response rates to these therapies are substantial (Knupp et al., 2016), the cumulative long-term risk of IS relapse approaches 50% (Hayashi et al., 2016; Rajaraman et al., 2016). As enduring freedom from IS appears to be a prerequisite for favorable long-term cognitive outcomes (Riikonen, 2010), an effective strategy to prevent relapse would be of great value. Unfortunately, no successful approach to relapse prevention has been established (Rajaraman et al., 2016).

Although the short-term efficacy of VGB is inferior to the hormonal therapies in general (Knupp et al., 2016; Lux et al., 2004), VGB appears to be especially effective in the treatment of IS among children with tuberous sclerosis complex (TSC) (Chiron et al., 1997). However, despite this established efficacy (Appleton et al., 1999; Elterman et al., 2001), the use of VGB has been limited by the threat of permanent peripheral visual field loss (Eke et al., 1997; Vanhatalo et al., 2002) and MRI abnormalities (Dracopoulos et al., 2010; Hernández Vega et al., 2014; Pearl et al., 2009; Wheless et al., 2009). In particular, VGB has been linked to reversible—and usually asymptomatic—signal changes on T2-weighted and diffusion-weighted MRI, localized to the basal ganglia, thalami, brainstem tegmentum, and deep cerebellar nuclei. Although estimates of visual field loss vary substantially, risk appears to be lower among infants with treatment duration less than 12 months (Riikonen et al., 2015) and the risk of clinically meaningful vision loss is very low among children treated for infantile spasms (Schwarz et al., 2016). With regard to MRI abnormalities, the risk of toxicity is approximately 20–30% (Pearl et al., 2009; Wheless et al., 2009) and dependent on dose but not duration of therapy (Hussain et al., 2017b). Although there is consensus in the United States that vigabatrin is the first-line treatment of choice for TSC-associated IS, there is great variability in prescribed dosage and duration of therapy (Pellock et al., 2010). With the contemporary views that (1) risk of meaningful visual field loss is low, (2) risk of MRI abnormalities may be reduced by avoidance of high dosage, and (3) MRI abnormalities are reversible and usually asymptomatic, VGB may represent a reasonable treatment in the effort to prevent IS relapse. Accordingly, using a prospective cohort of children with TSC and IS—among whom long-term VGB therapy is common—we set out to determine whether ongoing VGB treatment is associated with lower risk of IS relapse.

2. Method

2.1. Standard protocol approvals

This study was approved by the institutional review boards at each center. All patients' guardians provided written informed consent prior to any study procedures.

2.2. Study design and procedures

We conducted a nested cohort analysis. The patients comprising the nested cohort were derived from two linked ongoing multicenter prospective observational studies (ClinicalTrials.gov: NCT01780441 and NCT02461459), which seek to identify genetic and electrophysiologic biomarkers of epilepsy, autism, and long-term neurodevelopmental outcomes in children with TSC. For the analyses in this study, we specifically identified the subset of patients with IS (based on seizure-diary) and response to VGB, as defined below, and as illustrated in Fig. 1. Importantly, although the evaluation of a potential association between VGB exposure and IS relapse was not a specific aim of these studies, the data from these cohorts presented an opportunity to readily address this question. Our hypothesis was that risk to IS relapse would be lower among infants with longer duration and higher dosage of VGB.

Both parent studies enrolled infants with a clinical or genetic diagnosis of TSC, and all patients underwent serial in-person evaluations at ages 0–2, 3, 6, 9, 12, 18, 24, and 36 months (NTC01780441) and at ages 1.5, 3, 4.5, 6, 9, 12, 18, and 24 months (NTC02461459). At each visit, there was detailed accounting of seizure burden (via seizure diaries) with classification and quantification of each seizure type, and detailed tabulation of all medication exposures. In addition, serial outpatient video-EEGs (1 h duration, awake and sleep) were performed at each visit and interpreted in a blinded fashion by a team of board-certified pediatric electroencephalograhers as follows: All studies were reviewed by at least MG and JMP. In the event of any inter-rater discrepancy, studies were then reviewed by JYW for adjudication. Although there was specific notation of the presence or absence of epileptic spasms and hypsarrhythmia at each visit, the video-EEGs performed in the course of this study were in addition to clinical EEGs obtained by treating physicians, and were not intended for verification of IS onset, response to therapy, or relapse on a clinical basis.

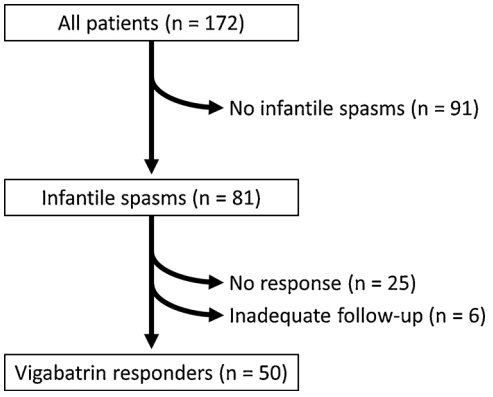

Fig. 1. Formation of the nested study cohort.
The analyses in the study are based on the 50 patients with infantile spasms who responded to VGB.

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