Epilepsy & Behavior 63 (2016) 79–88

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Cost-utility analysis of competing treatment strategies for drug-resistant epilepsy in children with Tuberous Sclerosis Complex

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ARTICLE INFO

Article history:
Received 17 May 2016
Revised 7 July 2016
Accepted 24 July 2016
Available online xxxx

Keywords:
Epilepsy
Seizures
Tuberous Sclerosis Complex
Antiseizure drugs
Ketogenic diet
Vagal nerve stimulator
Resective surgery

ABSTRACT

Background: The management of drug-resistant epilepsy in children with Tuberous Sclerosis Complex (TSC) is challenging because of the multitude of treatment options, wide range of associated costs, and uncertainty of seizure outcomes. The most cost-effective approach for children whose epilepsy has failed to improve with first-line medical therapy is uncertain.
Methods: A review of MEDLINE from 1990 to 2015 was conducted. A cost-utility analysis, from a third-party payer perspective, was performed for children with drug-resistant epilepsy that had failed to improve with 2 antiseizure drugs (ASDs) and that was amenable to resective epilepsy surgery, across a time-horizon of 5 years. Four strategies were included: (1) resective epilepsy surgery, (2) vagus nerve stimulator (VNS) implantation, (3) ketogenic diet, and (4) addition of a third ASD (specifically, carbamazepine). The incremental cost per quality-adjusted life year (QALY) gained was analyzed.
Results: Given a willingness-to-pay (WTP) of $100,000 per QALY, the addition of a third ASD ($6600 for a gain of 4.14 QALYs) was the most cost-effective treatment strategy. In a secondary analysis, if the child whose epilepsy had failed to improve with 3 ASDs, ketogenic diet, addition of a fourth ASD, and resective epilepsy surgery were incrementally cost-effective treatment strategies. Vagus nerve stimulator implantation was more expensive yet less effective than alternative strategies and should not be prioritized.
Conclusions: The addition of a third ASD is a universally cost-effective treatment option in the management of children with drug-resistant epilepsy that has failed to improve with 2 ASDs. For children whose epilepsy has failed to improve with 3 ASDs, the most cost-effective treatment depends on the health-care resources available reflected by the WTP.

1. Introduction

Tuberous Sclerosis Complex (TSC) is an autosomal dominant genetic multisystem disorder that is variably expressed with a prevalence of 1 in 10,000 and affecting approximately 50,000 individuals in the United States and over 1 million individuals worldwide [1,2]. It is one of the leading causes of genetic epilepsy, with seizures affecting almost 90% of children [3]. A third of these patients will be unable to achieve seizure freedom with antiseizure drugs (ASDs) alone [4,5].

The extended period that pediatric patients will live with epilepsy accrues to significant economic costs on the health-care system. An economic analysis is a set of formal methods to compare competing reatment strategies with respect to their resource use and their expected health outcomes. Jacoby et al. found that the cost of treatment is proportional to the severity of epilepsy [6]. In addition, more than half the total costs of epilepsy care are from the 15% of patients whose seizures are the most refractory to medications [6,7]. Furthermore, health-care costs for patients whose seizures are drug-resistant are eightfold higher than for those with controlled epilepsy [6].

Economic analysis in populations with pediatric epilepsy is rare, and the results from adults cannot be extrapolated to children for several important reasons, including the following: 1) varying underlying pathological substrates, 2) more common extratemporal pathology yielding lower seizure freedom outcomes, and 3) longer life expectancy increasing the impact of intervention on long-term costs and health utility. In a cohort of 30 pediatric patients with various underlying epilepsy substrates, Widjaja et al. demonstrated that surgical treatment

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http://dx.doi.org/10.1016/j.yebeh.2016.07.034
1525-5050/

in pediatric epilepsy was a cost-effective treatment strategy compared with continuing medical therapy [8].

The most effective and cost-effective treatment strategies for seizure control in children with DRE secondary to TSC must be established. This population is distinctively challenging to treat, because of a multitude of management options with significant clinical equipoise. The complexity of DRE treatment in children with TSC is compounded by the relatively modest surgical outcomes [9–11]. A cost-utility analysis (CUA) is warranted to evaluate the current interventions and to provide guidance to clinicians in treatment decision-making. Utilities capture the preferences individuals place for a particular health state, and the adjusted life expectancy (denominator in a CUA) is quality-adjusted life years (QALYs). Given the uncertainty on how best to select treatment strategies, the results of this study will assist clinicians in everyday decision-making and decision-makers in answering critical health policy questions. Some examples of health policy questions that can be answered include maximizing the benefits of health-care spending, containing costs, and providing bargaining power with suppliers of health-care products. Health-care resource-poor countries may decide not to fund some treatment strategies altogether given its high cost and low efficacy in consideration of their willingness to pay.

In this study, we compared 4 competing treatment strategies for DRE, as defined by the International League Against Epilepsy [12] in TSC: resective epilepsy surgery, vagus nerve stimulator (VNS) implantation, ketogenic diet treatment, and addition of a third ASD (specifically, carbamazepine). All these strategies are indicated treatment options of DRE in the pediatric population with TSC. Resective surgery is indicated for focal epilepsy, ideally in noneloquent cortex. Vagus nerve stimulator (VNS) implantation, approved for adolescents older than 12 years of age, is an adjunct palliative therapy to decrease seizure frequency. Ketogenic diet, a high fat, adequate protein, and low carbohydrate diet that leads to ketosis, is approved for children as a palliative approach. Additionally, in a secondary analysis, we investigated the role of mammalian target of rapamycin (mTOR) inhibitor as a potential treatment strategy for DRE in children with TSC. Although not clinically used for the treatment of DRE, mTOR inhibitors decrease proteins of the gene products regulated by TSC and are approved for the treatment of subependymal giant cell astrocytomas (SEGA) in patients with TSC. Preliminary data in Phase II trials demonstrated SEGA regression and modest improvement in seizures [13].

1.1. Objectives and hypothesis

Our primary objective was to evaluate the cost-utility of 4 competing antiseizure treatment strategies for children with focal DRE secondary to TSC that is amenable to surgery. Our secondary objective was to evaluate the cost-utility of treatment strategies for the same population of children, if a third ASD failed. In addition to ketogenic diet, VNS insertion, and surgical resection, our secondary analysis includes the addition of a fourth ASD and treatment with mTOR inhibitor. We sought to determine whether and under what circumstances one treatment strategy would be more cost-effective than another. We hypothesized that resective surgical treatment would be the costliest treatment initially but, in a 5-year timespan, would have the greatest health-utility compared with the alternative treatments.

2. Methods

2.1. Model overview

Using decision analysis software (TreeAge Software, Inc., Williamstown, Massachusetts, USA), our primary analysis evaluated a hypothetical cohort of children, under 18 years of age and being treated at a tertiary care hospital, with focal DRE secondary to TSC that is amenable to resective surgery. Patients entered the model having had seizures that did not improve from treatment with 2 first-line ASDs (valproic acid and levetiracetam) and receiving 1 of 4 competing treatment strategies for epilepsy: 1) addition of a third ASD (carbamazepine), 2) ketogenic diet, 3) vagus nerve stimulator (VNS) implantation, or 4) resective epilepsy surgery. The model included children whose epilepsy had failed to improve with valproic acid and levetiracetam, as these are first-line therapies for epilepsy associated with TSC because of high efficacy and tolerable side effect profiles. Our secondary analysis evaluated the same cohort of children with seizures refractory to 3 first-line ASDs; the analysis additionally included a fourth ASD (clobazam) and a fifth treatment: mammalian target of rapamycin (mTOR) inhibitor. We followed the hypothetical cohort over a 5-year time horizon following the initiation of treatment. We did not perform our analysis over a longer time period given the greater uncertainties associated with our key parameter estimates. The decision tree structure is described in detail in Appendix 1. The study was performed in accordance with the guidelines established by the US Public Health Service [14].

2.2. Model assumptions

For the reference case analysis, several assumptions regarding the treatment strategies, outcomes, and adherence were required. For model simplicity, we assumed full medical adherence, no adverse events from medical or interventional procedures, and no major complications or death. Furthermore, despite significant pharmacotherapy clinical equipoise, we assume that the first-line ASDs are valproic acid and levetiracetam, the third ASD is carbamazepine, and the fourth ASD is clobazam. This decision was informed by a study that described the most commonly used ASDs, excluding vigabatrin as it is commonly utilized for infantile spasms, in the treatment of epilepsy in children with TSC [15]. These assumptions with accompanying rationales are presented in Appendix 2. Some of these assumptions, as indicated in Table 6, were tested through sensitivity analysis.

2.3. Clinical probability estimates

Outcome probability estimates were retrieved using a review of the medical literature using MEDLINE that aimed to identify relevant publications between January 2000 and September 2015 in any language. We used keyword searches and reviewed the bibliographies of relevant articles to identify additional relevant articles. We utilized meta-analyses preferentially when available and, alternatively, large observational cohort studies to inform our parameter estimates. The key parameters used in the decision model and their respective citations are provided in Table 2.

2.4. Outcomes

In this CUA, our only outcome was QALYs since this is a measure that can be used to compare different interventions in medicine. Quality-adjusted life years (QALYs) were calculated using health utilities (corresponding to Engel classification at 1-year following the initiation of therapy) multiplied over a 5-year time horizon [16]. The basic event pathway created for this study assumes 4 possible outcomes following each treatment (i.e., Engel classes I, II, III, and IV outcomes) with the exception of the addition of a third ASD that leads to only 2 possible outcomes (i.e., seizure freedom and continuation of seizures). Our analysis reports the incremental cost-utility among the treatment strategies.

2.5. Utilities

Utility estimates were derived using the Cost Effectiveness Analysis Registry from the Tufts Medical Center website [17]. Table 3 contains the specific health utility estimates that were used.