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Review article

Treatment of benign focal epilepsies in children: When and how should be treated?

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Abstract

Benign focal epilepsies represent almost one-fourth of all childhood epilepsies and are a frequent occurrence in clinical practice. They include benign infantile seizures (BIS), Panayiotopoulos syndrome (PS), and benign childhood epilepsy with centrotemporal spikes (BCECTS) in this order of the onset age. Because the prognosis is always excellent in patients with benign focal epilepsies, we must consider the risks and benefits of chronic antiepileptic drug (AED) administration. AED treatment is usually not recommended for the patients with a first attack, but should be considered for those with a second or third attack. A choice of AED has been based on the expert opinion. Carbamazepine (CBZ) is recommended for both acute and chronic treatment of seizure clusters in patients with BIS. Valproic acid (VPA), CBZ or clobazam (CLB) appears to be a first option of AED for patients with PS. A common first choice for BCECTS is CBZ in the USA and Japan, and VPA in the EU. The treatment period should be as short as possible without waiting for EEG normalization, possibly within 2 years after the initiation of AED. We must remember that some patients with BCECTS may have an "atypical evolution". In conclusion, when and how to treat this benign condition should be determined in an individual manner based on the length and frequency of seizures, circadian rhythm of the attacks, interictal EEG findings, cognitive and behavioral functions in daily life and the attitude of the parents toward seizure recurrences and AED side effects.

Keywords: Antiepileptic drug treatment; Benign focal epilepsies; Benign infantile seizures; Panayiotopoulos syndrome; Benign childhood epilepsy with centrotemporal spike

1. Introduction

Benign focal epilepsies represent almost one-fourth of all childhood epilepsies and are most frequently encountered not only in the clinical setting of pediatric neurology, but also in pediatric emergency medicine [1]. Compared to children with intractable epilepsy, those with benign focal epilepsies are believed to enter remission without antiepileptic drug (AED) treatment until adolescence [1–4]. The risks associated with chronic AED treatment might outweigh the risks seizure recurrences because the patients may experience only a few such recurrences. Thus, the issue of when and how to treat the patients has been a matter of debate for many years [2,3,5]. Consensus has been generally established in the context of the treatment of the child with a first unprovoked seizure in that patients without specific risk factors are recommended to postpone AED treatment at least until a second seizure [6]. In addition, there have been few evidence-based studies for the treatment of benign focal epilepsies, which makes it difficult to develop a formulated treatment policy [3,7]. In this article, I focus on the treatment of following three representative benign focal epilepsies, benign infantile seizures (BIS), Panayiotopoulos syndrome (PS) and benign childhood epilepsy with

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centrotemporal spikes (BCECTS), because the prognosis of Gastaut type late-onset childhood occipital epilepsy has been shown to be unpredictable and the term "benign" is not included in this descriptive terminology [1].

2. Treatment for BIS

The concept of benign infantile convulsions (BIC) was first described by Fukuyama in 1963 [8]. He identified a group of previously normal infants who experienced one or a few clusters of generalized tonic-clinic seizures (GTCS), and later, the infants did not develop epilepsy. However, there was no progress for the concept of BIC until 1981 when Morooka reported 22 infants between 6 months and 2 years and 6 months of age who experienced a cluster of GTCS during periods of gastroenteritis with mild diarrhea [9]. This new syndrome received attention because of the close relationship between the seizures and rota gastroenteritis as well as the high incidence of this syndrome. In contrast, Watanabe et al. studied BIC with focal onset or secondarily generalized seizures from 1987 to early 1990's and proposed the concept of benign partial epilepsy in infancy, which was finally recognized as BIS in the 2001 International League Against Epilepsy (ILAE) classification [10]. At the same time, the syndrome of benign familial infantile convulsions (BFIS) proposed by Vigevano et al. was also recognized [11]. In the 2006 ILAE classification proposal, these two syndromes were combined and unified into one entity called BIS. Most recently, a new form of benign focal epilepsy termed benign familial neonatal-infantile seizures (BFNIS) has been established clinically and genetically, with an onset age between 2 days and 3.5 months of age, which nosologically link BIS to benign familial neonatal convulsions [12].

Thus, BIC as originally proposed by Fukuyama, came to include BIS and BIC with mild diarrhea, the latter of which has been recently re-designated as BIC with mild gastroenteritis (BICMG) and categorized as "chanced epilepsy". BICMG has not been recognized world-wide despite the fact that these seizures are the most common form of BIC in Japan. Sakauchi previously studied 56 infants with BIC, who showed two distinct peaks of onset age [13]. The earlier onset group was 2–11 months old, and they tended to have recurrent seizures or clusters of seizures that indicated BIS. In contrast, the later onset group was 1–2 years of age, and they experienced only one episode or one cluster of seizures, which indicated BICGM. Thus, the onset age and the association of mild diarrhea appear to be important for distinguish both conditions. The historical changes in the concept and terminology of BIS are shown in Fig. 1.

The treatments for BIS and BICMG can be categorized as acute or chronic (Table 1). Because the patients experience a cluster of seizures for several days, acute

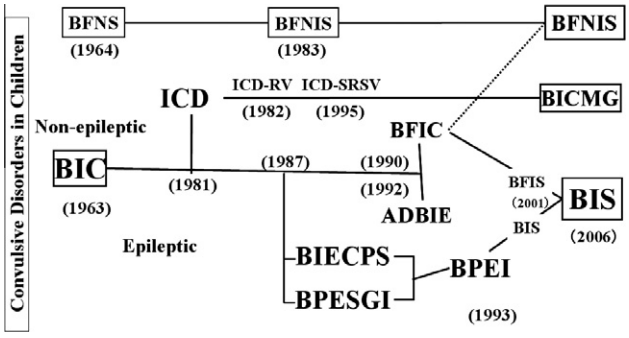

Fig. 1. Changes in the concept and terminology of benign infantile seizures (BIS)** by courtesy of Dr. Sakauchi. Abbreviations: BIC, benign infantile convulsions; ICD, infantile convulsions with diarrhea, ICD-RV, ICD with rotavirus infection; FCD-RV, febrile convulsions with diarrhea due to RV; BFIC, benign familial infantile convulsions; ADBIE, autosomal dominant benign infantile epilepsy; BPEI, benign partial epilepsy in infancy; BIECPS, benign infantile epilepsy with CPS; BPESGI, benign partial epilepsy with SG in infancy; BFNIS, Benign familial neonatal–infantile seizures; BICMG, Benign infantile convulsions with mild gastroenteritis.

treatment is urgent. There have been no control studies regarding the acute treatment for either syndrome. Intravenous or rectal diazepam therapy has been shown to be ineffective for seizure clusters [14–16]. There have been no systematic studies regarding rectal phenobarbital suppositories or intravenous phenytoin therapy. Intravenous lidocaine infusion therapy has been shown to suppress seizures effectively in a few open studies [14,15]. Most recently, single, low-dose oral CBZ has been shown control a cluster of seizures in patients with both BIS and BICGM. As such, CBZ appears to be the safest and easiest treatment option [16]. Although the evidence is limited, a single oral dosage of CBZ and an intravenous lidocaine infusion are currently recommended for the acute treatment of these seizures.

As for chronic prophylactic treatment, it is not generally recommended for patients with BICMG because the seizures seldom recur. In contrast, seizures in infants with BIS generally continue for months or years. The best AED and the best treatment duration have not been determined, although there was one open study recommending the use of low-dose CBZ in patients up to 2–3 years of age [16]. There were no available data for other agents such as PB or VPA, which have also been frequently used for infants with recurrent seizures. Thus, CBZ appears to be a first choice not only for the acute treatment of BICGM, but also chronic treatment of BIS.

3. Treatment for PS

PS is a benign age-related focal seizure disorder that occurs in early and mid-childhood. The onset age of epilepsy ranges from 1 to 14 years of age, with three-quarter of the cases occurring between 3 and 6 years. Clinical