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Catastrophic epilepsies: Medical and surgical treatment

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Abstract

Catastrophic epilepsies of infancy include several syndromes with disabling frequent seizures and development delay. They include specific epileptic encephalopathies like West and Dravet's syndrome, and less specific symptomatic partial and generalised epilepsies secondary to certain etiologies like tuberous sclerosis, Sturge Weber syndrome, focal cortical dysplasia and hemimegalencephaly. Effective treatment should control seizures and improve EEG abnormalities. Current treatment options are presented.

Catastrophic epilepsies of infancy include several syndromes with not only disabling frequent seizures but also major effects on normal development. Many of these are specific epileptic encephalopathies like West and Dravet's syndrome with age-dependant expression, predictable responses to antiepileptic drugs and expected outcomes. Sometimes less specific symptomatic partial and generalised epilepsies may have a similar catastrophic course especially if these are secondary to certain etiologies like tuberous sclerosis, Sturge Weber syndrome, focal cortical dysplasia and hemimegalencephaly.

Management is a daunting task as an effective treatment should not only control seizures and status epilepticus, but also improve EEG abnormalities if any meaningful gains in development are to be made. The disorders discussed here include the early infantile epileptic encephalopathies with suppression - burst (EIEE, Ohtahara's syndrome), early myoclonic encephalopathy (EME, Aicardi's syndrome), West syndrome, Dravet's and related syndromes, malignant migrating partial seizures of infancy (Coppola), remote symptomatic partial and generalized epilepsies.

EARLY INFANTILE EPILEPTIC ENCEPHALOPATHIES WITH SUPPRESSION - BURST (EIEE, OHTAHARA's SYNDROME), EARLY MYOCLONIC ENCEPHALOPATHY (EME, AICARDI'S SYNDROME)

There is no effective therapy for EIEE and EME. Antiepileptic drugs and even ACTH and steroids cannot alter the poor prognosis. Some seizure reduction has been reported in case reports of EIEE with phenobarbital, zonisamide[1] and pyridoxine.[2] EIEE is often due to structural brain diseases and surgical resections have been shown to be beneficial in hemimegalencephaly and focal cortical dysplasia.[3] EME has a more dismal outcome despite all treatments. Trying pyridoxine however, is always justified in cases of EME.

WEST SYNDROME

Major advances in management include the use of ACTH[4-7](1958), vigabatrin[8-10] (1990) and the concept that focal lesions often underlie this 'generalised' syndrome and therefore being amenable to surgical resection.[11] There is still no clear agreement in which agent to use initially, with ACTH being popular in the USA and Taiwan, vigabatrin in Europe and Korea, and pyridoxine in Japan. In India and other developing countries, prednisolone and valproate are used frequently probably because of low cost and easy availability.

There is a spontaneous remission rate in West syndrome of about 25% by 1 year of onset[12] and this must be taken into account when evaluating new antiepileptic drugs.

Standard dose prednisone has been shown to have lower response rates (29-33%) compared to ACTH (42-87%) in two randomized controlled trials[4,5], though results reached significance in only one.[5] On further analysis it is apparent that ACTH given within a month of onset of spasms has a higher response rate than if it is given later. In a recent study using higher doses of prednisone (40 mg/day), response rates were similar between ACTH (76%) and prednisone (70%).[6,7] ACTH dosage, treatment duration and what type of preparation to use are areas of debate. Natural ACTH is less potent than it's synthetic form, and has fewer adverse effects; hence dosage

is much higher. Vigabatrin has been shown to be an effective treatment[8,10] though steroids / ACTH have higher spasm freedom rates, and higher rates of EEG improvement in the short term.[6] Also vigabatrin acts slower with maximum effect sometimes taking 3 months. Outcomes at one year are similar with both steroids and vigabatrin, except in the subgroup of cryptogenic spasms, where the group given steroids / ACTH has better developmental scores.[7] Vigabatrin is now established in tuberous sclerosis associated spasms, with dramatic effects at low doses seen in greater than 90%.[9] The risk of visual field defects with vigabatrin[13] has made several authors limit it's use to 3-6 months without any compromise on spasm freedom rates. Nitrazepam[14], high-dose valproate[15] (100-300 mg/dl)) and recently sulthiame[16] have been shown in to be effective.

Other antiepileptic drugs without strong evidence of efficacy include clonazepam, pyridoxine, topiramate, lamotrigine, zonisamide and ganaxolone.[17] IVIG, ketogenic diet[18] and surgical resection are options in refractory cases.[11]

Developmental outcomes have been shown to benefit from spasm control with better outcomes in cryptogenic West syndrome vis-à-vis symptomatic West syndrome. Gains in visual and auditory attention occur even in symptomatic West syndrome, as has been shown in spasms associated with Down's syndrome[19], tuberous sclerosis[20], and in those controlled by surgical resection.[21]

DRAVET'S SYNDROME

Therapy is disappointing with conventional antiepileptic drugs alone in this genetic syndrome associated with SCN1A mutations. Frequent status epilepticus and later myoclonic and other seizures are probably at least partly responsible for the inevitable mental retardation that follows. Though recently controlled trials support the use of topiramate[22] and stiripentol[23] used along with valproate and clobazam, these have not yet been shown to affect the bad developmental outcome. Ketogenic diet has also been used with some beneficial effect. Carbamazepine and lamotrigine[24] have been shown to worsen seizures and should be avoided.

MIGRATING PARTIAL EPILEPSY OF INFANCY

This devastating neonatal and early infantile-onset syndrome presents with frequent partial seizures, developmental arrest and microcephaly. Virtually all antiepileptic drugs are ineffective though case reports support the use of levetiracetam[25] and bromides.[26]

CATASTROPHIC PARTIAL EPILEPSIES

The experience with the newer antiepileptic drugs like topiramate[27] and oxcarbamazepine[28] are promising. Surgical options have been developed in symptomatic epilepsies associated with focal cortical dysplasia and hemimegalencephaly[29], and even in multifocal disorders like tuberous sclerosis[30] with reasonable results. Sturge Weber syndrome in infancy often lead to deficits[31], and early surgery has been shown to help.[32] Aspirin may reduce the need for surgery in severe Sturge Weber syndrome.[31]

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