LEADING ARTICLE

EPILEPSY IN INFANCY

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Convulsive disorders in infancy may be either epileptic or non-epileptic in nature.

The majority of convulsions occur when the essentially normal brain is subjected to a variety of stresses and stimuli, but the propensity to develop seizures is determined, at least in part, by genetic or constitutional factors. Such convulsions are called OCCASIONAL SEIZURES because they occur only in response to provoking circumstances, and must be distinguished from epilepsy, which is a chronic, spontaneously recurring group of conditions. The classical example of occasional seizures is that of FEBRILE CONVULSIONS, which occur only in response to a rise in body temperature. The outcome and different courses following febrile convulsions during the first year and those with later onset have been studied and reported by Lennox-Buchthal (1), and more recently by Nelson and Ellenberg (2). Occasional seizures other than febrile convulsions are the results of acute insult to the brain or disturbances in homeostasis originating outside the CNS. The main causes are intracranial infections, head trauma with or without intracranial haemorrhage, metabolic disturbances like hypoglycaemia, hypocalcaemie, and electrolyte imbalance, acute or chronic intoxications, acute cerebral anoxia, cerebro-vascualr accidents, and other forms of encephalopathies. The occurrence of occasional seizures is concentrated in infancy and early childhood because the brain may be more sensitive to certain stimuli (especially fever), and many of the responsible disorders take place predominantly during this period of life.

The incidence of epilepsy is higher during the first year of life than during any other subsequent preiod. Epilepsies in the first year of life, outside the neonatal period, have been considered the gold mine for future research, as much remain unknown about this heterogeneous group of convulsive disorders. Apart from infantile spasms which are an unique form of seizure disorder limited almost entirely to infants during the first year of life, a high proportion of the epilepsies that begin before the age of one year do not belong to any recognisable epileptic syndromes and are currently unclassifiable according to the International Classification of Epileptic Seizures (3). These non-specific seizures are atypical and often limited in their clinical presentations. They consist of mild changes in muscle tone, staring spells or blank looks, twitching of eyelids, eye deviation, lip smacking episodes, clenching of fists, and autonomic manifestations such as flushing of face, pallor, circumoral cyanosis, or disturbances in respiratory and/or cardiac rhythms. Various combinations of these symptoms may produce a great variety of seizure patterns that defy inclusion in any precise category. Using polygraphic and video monitoring, it has been shown that a vast number of such attacks may easily be missed by inexperienced parents or doctors (4). The EEG patterns may not be consistent with the clinical seizures. Focal discharges have been recorded in infants with bilateral motor phenomena or with autonomic or atypical manifestations. Unilateral predominance over one hemisphere is common. Generalised seizures are most commonly purely tonic or clonic in type, and almost never present as classical tonic-clonic seizures. These atypical clinical manifestations are probably related to the special neurophysiological properties of the developing brain, in particular to the incomplete development of interhemispheric and synaptic connections. The rapidly changing state of brain maturation is also responsible for modification of seizure types with time in the same patient. The atypical seizures often evolve into more characteristic attacks as the child grows older. Thus, early epilepsies manifested initially by atypical attacks may be replaced later by fits more specific for recognised epileptic syndromes such as Lennox-Gastaut syndrome. Tumours of the temporal lobe can produce atypical attacks in infants and develop later into typical temporal lobe seizures.

Infantile epilepsies have multiple causes, and it is generally accepted that the epilepsies of early infancy are most often the results of organic brain damage. The aetiological factors can be prenatal, perinatal, and postnatal in origin. They can be in the form of hypoxic-ischaemic insults, infections, trauma and haemorrhage, metabolic and toxic disorders, neurocutaneous syndromes and other cerebral malformations. Epilepsies in infancy can also be divided into symptomatic and cryptogenic groups. The SYMPTOMATIC group includes those infants with abnormal mental and/or neurological development prior to the onset of epilepsy, and those with evidence of a brain lesion of clinical or neuro-radiological examination. The CRYPTOGENIC group, on the other hand, includes those cases in which, in addition to the lack of detectable causes, psychomotor development has been normal until the onset of the seizures. The distinction between symptomatic and cryptogenic epilepsies is of great practical significance because a poor prognosis is to be expected in patients with structural brain damage. However, classification of a particular patient is always fraught with difficulties, especially if early development is accepted as a criterion, because historical data on infant development are notoriously unreliable. Moreover, classification depends on the extent of the investigations performed and on the nature of the lesion and the ease with which it may be detected. The apparent

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absence of brain lesions does not preclude their existence, and undetectable brain damage might explain the poor outcome of apparently cryptogenic cases. These uncertainties are reflected in the different proportions for symptomatic epilepsies in the literature, and the improvement of diagnostic techniques is shown by the diminishing proportion of cryptogenic cases.

Three recent hospital-based studies have increased our understanding of the first-year epilepsies, and their results are generally comparable. (5, 6, 7, 8, 9). Chronic seizure disorders beginning before the age of 1 year are classified according to seizure type as infantile spasms, status epilepticus (i.e., any seizure lasting 30 minutes or more), and the non-specific atypical seizures. The latter are further subdivided into generalised and partial on the basis of the ictal clinical symptoms. Those seizures featuring any localised or lateralised motor symptom, whether effecting face or limbs or involving deviation of the head or eyes, are classified as 'partial'. In their absence, a seizure is considered as 'generalised' although, admittedly, such seizures can result from either diffuse or partial discharges. These syndrome groupings may seem arbitrary, but they do provide a useful framework for studying the clinical course of infantile epilepsies.

INFANTILE SPASMS (West's syndrome) are a remarkable, strongly age-dependent epileptic syndrome. The syndrome occurs almost exclusively during the first year of life. In almost all patients, the characteristic spasms are associated with mental retardation or deterioration and in a majority with a striking EEG pattern called hypsarrhythmia. The prognosis for children with infantile spasms remains grave. Mortality is about 20% and in survivors, cerebral palsy is present in one-third to one-half of affected children. Mental retardation is observed in 80% of patients and is of a severe degree in more than 50% of patients. Psychiatric disorders, e.g. autism, affect 30% of the patients, and may be present even in patients of normal intelligence. Persistent epilepsy, in the form of other types of seizures following infantile spasms, occurs in about 60% of children followed up for several years. Lennox-Gastaut syndrome and epilepsy with partial complex seizures are the most common forms. About 60% of infantile spasms are syptomatic and 40% are cryptogenic. The gloomy prognosis holds for nearly all the symptomatic forms and for more than half the cryptogenic ones.

Infants with STATUS EPILEPTICUS have the highest mortality. Recurrence or persistent epilepsy develops in 70-80% of cases. The epilepsy is usually partial, and especially the complex type, and is hardest to control with drugs. Mental and neurological development are affected in two-thirds of cases, but less than that for infantile spasms. The prognosis is better when the EEG is normal in the first year, but worse when the onset is early and there is recurrence. The poor outcome of status epilepticus may be due to the known fact that long-lasting seizures can induce brain lesions which are responsible, at least in part, for deaths and sequelae.

The outcome in the non-specific ATYPICAL group also reveals certain trends. Two-thirds of these cases developed epilepsy, considerably more than in the group with infantile spasms, but little less frequent than those with status epilepticus. When they are cryptogenic, the effect on mental and neurological development is generally less serious and less frequent, whereas three-quarters of those with symptomtic forms had abnormal mental development, as did almost all of those who developed epilepsy. The prognosis will be gloomier if, during the first year, the EEG shows epileptic pattern and seizures recur. According to Cavazzuti et al (8), whether the first seizures are generalised or partial does not seem to affect the subsequent development of epilepsy, whereas Chevrie and Aicardi (7) found a higher incidence with partial attacks. However, all agreed that mental and neurological development was noticeably better after generalised seizures. The less favourable outcome after partial seizures is probably the result of more extensive brain damage. A severely damaged brain may be unable to produce relatively well orgainsed, generalised seizures. Indeed, partial seizures were most frequent in patients with neurodevelopmental retardation antedating the first seizure or with demonstrable brain pathology, whereas generalised seizures were more common in infants with cryptogenic seizures. On the other hand, in all groups there are patients who do not develop epilepsy or neurological or mental impairment. Factors for a more favourable prognosis are cryptogenic sejzures, a normal first EEG pattern, onset of seizures in the second six months of life, a single seizure and, in the case of atypical seizure types, a generalised seizure. The prognostic factors do not apply the same way to all groups. For example, over half the cases with cryptogenic status epilepticus or infantile spasms became mentally retarded, possibly because of damage by the seizures themselves. Moreover, the cryptogenic nature of the seizures does not noticeably reduce the chances of developing epilepsy among those who suffered status eilepticus or atypical seizures.

A family history of epilepsy or of convulsions is more common in atypical seizures than in infantile spasms. The proportion of positive family histories is higher in patients with generalised seizures, especially when they are of cryptogenic origin. This suggests that genetic factors play a role in the aetiology of infantile seizures, the contribution of genetic factors being highest in cases of cryptogenic bilateral seizures and lowest in those of partial symptomatic attacks.

Infantile spasms are notoriously resistant to conventional anticonvulsant drugs. ACTH and corticosteroids have been the most popular treatment for infantile spasms and is effective for the spasms and the EEG abnormalities. Its effectiveness is probably greater than that of anticonvulsants, like benzodiazepines such as nitrazepam, and sodium valproate. The long-term efficacy of hormonal treatment on mental development and on later epilepsy has not been established conclusively. Anticonvulsant treatment is used as an adjunct to hormonal therapy or when hormonal treatment has failed and in obviously brain-damaged patients.

The treatment of the other epilepsies of early onset is basically the same as that of later epilepsies and rests on the use of anti-epileptic drugs. Phenobarbitone seems to be still widely used in this age range, but carbamazepines and the benzodiazepines have also been used. Phenytoin is particularly difficult to handle in infants because of its non-linear pharmacokinetics. Sodium valproate has been successfully used in some patients, but may be more dangerous in infants, and most hepatotoxic accidents have been reported in children less than 2 or 3 years old. The metabolism of anticonvulsants is dependent on the age of the patients. In general, neonates slowly metabolise anticonvulsants and become easily intoxicated. After a few weeks, the metabolic rate of most drugs increases to such an extent that optimal blood levels are difficult to attain, even using large doses, and poor control is therefore quite frequent. Thereafter, dose requirements progressively diminish as the metabolism of drugs slowly becomes less rapid. Special care is required to avoid side effects, which easily go unrecognised in small children. Blood level determination is therefore more frequently useful in infants than in older children. Pyridoxine dependency should always be considered in status epilepticus and in other seizures resistant to control. This disorder may manifest itself up to more than one year of age and with any type of seizures (10), and a therapeutic test is the only way of establishing the diagnosis. The prognosis of epilepsy in infancy is usually grave even though reports from specialised centres tend to make it excessively pessimistic. Treatment is problematic, unsatisfactory, and the outcome of whatever form of therapy is largely unknown. Prevention is therefore of utmost importance.

The article 'Epilepsy in infancy' in this issue of the Singapore Medical Journal, from Hospital Universiti Sains, Kelantan, Malaysia, further demonstrated the poor outcome of infantile epilepsies. In their study, the most striking feature has been documentation of birth asphyxia, or other perinatal factors such as neonatal meningitis, neonatal hypoglycaemia, kernicterus and intrauterine infections, to be responsible for 60% of the infantile seizures. As high as 80% of the deliveries in the States of Kelantan are conducted at homes by unskilled village midwives, and nearly a quarter of the total admissions to the newborn nursery was formed by newborns with birth asphyxia or respiratory distress. All these mishaps are avoidable and can be preventable. Proper organisation and regionalisation of perinatal care will not only ensure the highest success rate in every reproductive endeavour, but also reduce the incidence of future morbidities like infantile epilepsies.

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