Personal Practice

Infantile Spasms

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Infantile spasm is characterized by massive epileptic myoclonus which typically begins before 6 month of age. Infantile spasms occur in approximately one in every 3000-4000 children. This condition was first described by West in 1981(1). The West's syndrome consists of a triad of infantile spasm, mental retardation and characteristic electroencephalographic (EEG) abnormality. The latest (1989)(2) International Classification of Epilepsy and Epileptic Syndrome categorizes this disorder as generalized epilepsy. In majority of cases the affected children have normal prior development and do not have any obvious etiology or previous risk factors.

Classification

Patients with infantile spasms are classified into one of the three etiologic groups: symptomatic, cryptogenic and idiopathic. The symptomatic group includes the patients in whom an underlying neurological disorder has been identified, for example tuberous sclerosis or cortical dysplasia. Classification as cryptogenic indicates that no specific cause has been identified but child was not developmentally normal prior to onset of seizures, thus, an underlying brain abnormality can be presumed. Idiopathic term is for infants who were neurologically normal prior to onset of infantile spasm and in whom no underlying cause can be identified. The identification of patients of cryptogenic group is particularly important because early diagnosis and vigorous treatment may reverse the etiopathogenic cause and may even bring subsequent normal intellectual development in few cases.

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Etiopathogenesis

It is being thought that infantile spasm is a non-specific reaction of the developing brain to a wide variety of insults. It seems likely that the condition is more age specific than disease specific. Adverse perinatal events are the most commonly identified predisposing factors. Of the various perinatal factors, cerebral hypoxia or anoxia have been most frequently implicated. Difficult deliveries, intracranial hemorrhage, hypoglycemia, kernicterus and septicemia were also noted to be of etiological importance. The pathological findings in the brains of 214 patients reported in previous publications were reviewed by Jellinger(3). He classified them into: *(i)* Embryofetal lesions (malformations and metabolic diseases); *(ii)* Peri-postnatal lesions; (*iii*) Embryofetal plus peri-postnatal lesions; *(iv)* Negative findings; and *(v)* Acute lesions or unknown. Aicardi syndrome (absence of corpus callosum, choreoretinitis and severe mental retardation) is an important example of a congenital cause of infantile spasm. Others are immature dendritic development(4), hydra-ncephaly, and Down's syndrome. Prenatally, genetically determined metabolic and degenerative disorders can cause infantile spasms *(e.g.,*

leucodystrophies, Leigh's disease, phenylketonuria and Alper's disease). During investigation of infantile spasms, if no definitive cerebral structural abnormalities are visualized, a full metabolic workup is indicated.

Among cerebral malformations, which account for one third of all autopsy cases, lissencephaly (agyria-pachygyria) is a common finding. However, lesser degrees of abnormality of neuronal migration including heterotopias and minor cortical dysplasias are more frequent. Peri-and postnatal lesions include porencephaly, periventricular leukomalacia and generalized atrophy. Combined embryofetal and peri-postnatal lesions are under reported. Infantile spasms secondary to meningitis or encephalitis account for only a small proportion of infants who come for autopsy(5,6). The neuropathological examination of surgically resected tissue from these patients was helpful in improving our understanding of cortical abnormalities associated with infantile spasms. Vinters *et al.(7)* reported histopathological findings of 15 patients. They observed that findings could be divided into two groups namely, malformative lesions and destructive lesions. Ten of the 13 patients had dysplastic or hamartomatous lesions, 4 had cystic-gliottic encephalopathy, 2 had both and one patient had normal appearing cerebral cortex and subcortical white matter.

Immunization and Infantile Spasms

The role of pertussis immunization as a causative or associated precipitant in the production of infantile spasms has been argued extensively(8). The main feature leading to suggestion that any causal relationship or association exists between pertussis immunization and infantile spasms is clustering of case recognition within a few days after immunization. Now, contrary to earlier suggestions, experts believe that immunization is rarely, if ever, the cause of infantile spasms. It most likely acts in association with other unidentified factors to precipitate clinical manifestations in already predisposed children(9).

Clinical Manifestations

Clinically, infantile spasms are characterized by sudden bilateral symmetrical contraction of muscles. There are three main types of infantile spasms: flexor, extensor, and mixed flexor-extensor. Mixed forms of spasms are the most common type (42%) followed by flexor spasms (34%) while extensor spasms are the least common (23%). Most infants with this disorder have more than one type of spasm, and the type observed at any given moment may be influenced by body position. In flexor spasm, simultaneous flexion of neck and trunk occurs. Flexion, abduction or adduction of upper limbs and flexion and adduction of lower limbs occur simultaneously. Extensor spasms occur when extensor muscles are predominantly involved. These spasms consist of abrupt extension of neck and trunk, with extension and abduction or adduction of the arms or legs. Mixed flexor-extensor spasms consist of flexion of the neck, trunk and arms with extension of leg, or less commonly flexion of legs and extension of arms. The child becomes irritable, cries, and is difficult to feed. When picked up he/she will frequently hyperextend the neck and back. The child loses interest in the environment. Usually, the mother first notices clusters of flexion spasms or startle responses in association with crying. The episodes are most frequent when child first awakens in the morning. Videotelemetry has revealed that some children have very subtle variants of spasms, missed by the parents which usually either coexist with typical spasms or follow their apparent cessation after treatment. It is seen that infants who develop spasms have a cessation of

normal psychosocial development and frequently show a developmental deterioration as spasms continue to occur. Motor performance may be affected to a less degree than adaptive behavior. The skin should be searched for ash-leaf patches of depigmentation most commonly seen on back of trunk and legs which would suggest tuberous sclerosis. The shape of skull may be suggestive of an underlying malformation, for example, porencephalic cyst. Stigmata of metabolic disease, such as failure to thrive, vomiting, rashes, and unusual smelling urine should also be sought. When spasms are symptomatic of mitochondrial cytopathy, the infants are extremely hypotonic(6,8,10).

Electroencephalography (EEG)

A variety of EEG findings may be seen at the time when a patient is having infantile spasms. These findings include normal background activity, diffuse slowing of the background rhythms, generalized slow wave and spike activity, and focal and multifocal spikes and sharp waves. However, the most characteristic pattern usually associated with infantile spasm is hypsarrhythmia.

Hypsarrhythmia has originally been described as random high voltage slow waves and spikes. These spikes vary from moment to moment, both in duration and location. At times they appear to be focal and few seconds later they seem to originate from multiple foci. Occasionally the spike discharge becomes generalized but it never appears as a rhythmically repetitive and highly organized pattern that could be confused with a discharge of the petitmal or petitmal variant type. The abnormality is almost continuous and in most cases is apparent both in awake as well as in the sleep records(11). Partial seizures occur before or simultaneously with infantile spasms in 51% of symptomatic and 33% of cryptogenic cases and are often associated with asymmetrical interictal pattern in EEG. Focal slow activity is commonly associated with a prenatal etiology. Focal abnormalities are easier to detect in EEG's obtained early in the course of illness. Once the hypsarrhythmic pattern is established, it is easy to miss subtle focal EEG abnormalities. Like infantile spasms, hypsarrhythmia is an age specific abnormality and may even be found in severely abnormal children in the same age group who do not have clinical syndrome of infantile spasm. Hypsarrhythmia persists for a time and then disappears with advancing age of the child and maturation of the nervous system and is replaced by a less disorganized pattern. An upper age limit for hypsarrhythmia has not been established but it is uncommon beyond the age of 3 years. The presence of hypsarrhythmia in an infant during first year of life is a sign of grave prognostic significance even if hot associated with infantile spasm(6,8,12).

Neuroimaging

Computed tomographic (CT) scanning is abnormal in 60-70% of children with infantile spasms and is equally likely to be abnormal in clinically cryptogenic or symptomatic cases. Focal lesions, including cerebrovascular lesions and rarely, brain tumors may be demonstrated in addition to more diffuse congenital malformation. Diffuse cerebral atrophy is a common finding. Magnetic resonance imaging (MRI) may demonstrate focal or diffuse abnormalities including neuronal migration defects. Findings may be non-specific *(e.g.,* periventricular hyperintensity or poor myelination). Pathological specimens from patients with infantile spasms may show cortical dysplasia. Gemistocytic ballooning, similar to that seen in tuberous sclerosis, is a common abnormality. These lesions may not be visible on MRI, particularly in infancy when the

lack of myelin means that there is less contrast between grey and white matter(13-15). However, the most sensitive neuroimaging tool for detectin of localized disturbances in these children is the positron emission tomography (PET) scan. Chugani *et* a/.(16) first reported that PET can detect cortical disturbances even when MRI and CT are normal.

Treatment

Hormonal Therapy

There are several reports suggesting that treatment of infantile spasms with ACTH results in cessation or marked reduction of the seizures, and disappearance of the hypsarrhythmic EEG pattern(6). Jeavons and Bower for the first time reported encouraging results with oral corticosteroids also(17). Early reports on successful control of seizures with subsequent good mental development have not been universally confirmed by subsequent studies. However, ACTH and oral corticosteroids still have an important place in the treatment of infantile spasms. Most workers have favored ACTH rather than steroids for initial therapy because it was claimed that a more rapid response was obtained with ACTH. The dosage of ACTH has varied from fairly moderate dosages (20-40 units/day) upto very high dosages (80-120 units/day). The initial administration of 40 units per day for 1-2 weeks followed by 20 units per day or 40 units alternate days for a further 2-3 weeks, followed by oral steroids therapy for upto 3 months, has been a widely recommended regimen. Prednisolone in an initial dose of 2 mg/kg per day or dexamethasone in a dose of 0.3 mg/kg per day have been used with gradual reductions in dosages to a maintenance level for a variable duration of therapy(6,8).

There is general agreement that patients who have normal development up to the onset of spasms and who have normal CT scans (cryptogenic variety) are most likely to respond to treatment. There are strong arguments against treating patients with obvious developmental delay or severe neurological abnormalities prior to onset of infantile spasms with ACTH or steroids, particularly if the spasms have been preceded by other seizures. Usually EEG improvement parallels clinical improvement and this becomes apparent in the second week of therapy. However, EEG improvement may occur without clinical improvement and vice versa. The long term outlook in the patients is very poor, even if their spasm are controlled, and side effects of steroid therapy (electrolyte imbalance, reversible hypertrophic obstructive cardiomyopathy and bacteremia) may even be fatal at times(18,19).

Pyridoxine

Pyridoxine has been reported to be beneficial in treating a small number of patients with infantile spasms. Due to lack of data based on controlled studies, it is difficult to draw a definite conclusion regarding role of pyridoxine. The dosages of pyridoxine varied significantly as did the route of administration. Some patients received orally and some parenterally and in few, the drug was given in combination. The number of doses of pyridoxine required to produce an effect is unclear. In some patients, a response was reported to occur within minutes of a single administration while in others it did not occur for many days after institution of therapy. However, a definitive statement regarding its efficacy in treating this disorder cannot be made until the results of appropriately designed and controlled studies are available(20,21).

Sodium Valproate

Jeavons(22) for the first time reported that valproate may reduce the frequency

and severity of infantile spasms. A study in which valproate was used in increasing dosage upto 100 mg/kg/day reported control in half the patients. However, muscle hypotonia, lethargy and vomiting were commonly present and thrombocytopenia was found in one third of cases. High dose sodium valproate at a dose of 200 mg/kg per day with or without vitamin B6 may be helpful in the management of intractable infantile spasms, although side effects may pose serious problems in few patients. A combination of valproate in moderate dosage (40 mg/kg reached over a week) together with hydrocortisone (15 mg/kg per day) controlled spasms in 90% of cryptogenic and 65% of symptomatic cases. Adding ACTH in resistant cases increased the response rate to 100% and 78%, respectively(23). Symptomatic patients with peri-ventricular leukomalacia, porencephaly or a postnatal etiology had a higher response rate than those with perinatal asphyxia.

Benzodiazepines

The benzodiazepine drugs particularly nitrazepam and clonazepam have been used with some success in controlling the spasms but without significant beneficial effect on intellectual outcome. However, tolerance usually develops rapidly. An initial dose of clonazepam 0.01-0.03 mg/kg per day is suggested, with subsequent dosage according to the individual patient's need. Approximately half of children with infantile spasms are reported to have responded to nitrazepam. The dose suggested is initially 0.5 or 1 mg/kg per day with adjustment to seizure control(6). In a study comparing nitrazepam to ACTH there was no significant difference between the two agents(24).

Other Antiepileptic Drugs

In a small number of patients with tuberous sclerosis, Chiron *et al.* (25) reported a successful outcome using vigabatrin to control infantile spasms. It has been suggested that vigabatrin should be the drug of choice in other symptomatic infantile spasms and perhaps in cryptogenic cases as side effects are less common than with ACTH. In many of these patients at follow up, partial seizures developed later and addition of carbamazepine was required to control seizures(26,27).

Epilepsy Surgery

Children who fail to respond to traditional medical therapies are candidate for surgical intervention. In contrast to ictal and interictal generalized EEG findings, selected patients with infantile spasms have areas of focal or regional hypometabolism on PET scan. In few patients of intractable infantile spasms with suggested focus on EEG also confirmed on PET (usually in parieto-occipito-temporal areas) may respond to respective surgery. These children are often found to have cortical dysplasia, and have a significant improvement in both development and seizure control after surgery(14,15).

Prognosis

The long term prognosis is dependent on the underlying condition. The prognosis for symptomatic infantile spasms is poor. In a study, the mean IQ of the patients who presented with symptomatic infantile spasm was 48.4, while the mean IQ for children who had cryptogenic infantile spasm was 71.2(28). A normal CT scan does not predict a good outcome although an abnormal CT scan is associated with poor prognosis. The role of early treatment in stopping spasms and improving intellectual outcome is controversial but may be crucial for-few cases. In natural course, approximately 25% patients remit spontaneously within 12 months from onset; however, only 9% of these untreated patients are nor-

mal at subsequent follow up. Approximately 20% of patients die within 7-12 years. Upto 64% of survivors have persisting epilepsy. Where seizures remit, 74% of patients are seizure free by age 5 years. Lennox-Gastaut syndrome follows in somewhat less than 25% of cases. Approximately 90% of survivors are mentally retarded(29-31).

Conclusion

Despite better understanding of disease and availability of newer effective anticonvulsants and option for epilepsy surgery, the long term prognosis remains poor for a majority of the patients with infantile spasms. The best prognosis is for children with cryptogenic infantile spasms who respond to ACTH. Better obstetrical and perinatal management may prevent infantile spasms in a few children.

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