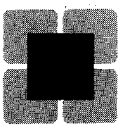

PANEL DISCUSSION

MELINDA ESTES, MD AND W. DOUGLAS KNOWLES, PHD, CO-MODERATORS; HERMANN DOOSE, MD; HEINZ-JOACHIM MEENCKE, MD; ELI M. MIZRAHI, MD; SOLOMAN MOSHÉ, MD

Question: Are changes in mesiotemporal sclerosis perhaps the result of febrile seizures early in life?

Dr. Meencke: No, it is our experience that mesiotemporal sclerosis and febrile convulsions are due to the same pathogenetic mechanism. In our cases, we have chiefly venous circulatory disturbances; these are due to mesiotemporal sclerosis and, at the same time, to febrile convulsions, if you have a genetic background or disposition.

Question: Are events thought to be brain stem seizures without EEG changes to be treated, and if so, how?

Dr. Mizrahi: At our institution, where we are able to monitor such babies on a 24-hour basis, we do not treat these events as epileptic seizures. The natural course of such clinical events is that they diminish spontaneously over time.

However, such events can be suppressed by anticonvulsants. This may be one of the reasons why, early on, they were thought to be of epileptic origin. Typically, very high dosages of anticonvulsants are required, so that the effect may be suppressive rather than antiepileptic.

In practice, we encourage identification at the bedside of those clinical events which are believed to be clearly epileptic in origin (i.e., focal clonic seizures) and initiate therapy at that point. If there is a question about the clinical event, we urge the physician to perform the clinical maneuvers we have described, either to evoke or suppress the events. If the behaviors can be elicited or suppressed by these maneuvers, then no treatment is instituted. This decision is confirmed by monitoring.

Question: What are the data showing that microdysgenesis is a pathologic finding? Specifically, what is the incidence in age-matched controls with neurologic symptoms? Were observers blinded to the clinical findings?

Dr. Meencke: Our discussion about the pathologic relevance of microdysgenesis starts from observations blind to different clinical syndromes. It is noteworthy that about 35% of the unselected patients with epileptic syndromes will demonstrate a form of microdysgenesis, compared to only 4% of normal controls. Specifically, we noted an incidence of microdysgenesis in normal controls of 3.8%; in early-death children, 10.3%; in epilepsy patients, 36%; and in children with peripheral maldevelopment, 67%. We now have a confirmation by the morphometric analysis and we can differentiate the extent of increase of neuron density in the different syndromes.

Question: Is there an autosomal dominant inheritance for some forms of absence seizures, or are they all polygenic?

Dr. Doose: The question does not have an unequivocal answer. One must remember that it is characteristic of polygenically determined diseases that they can look like autosomally transmitted diseases with incomplete penetrance. As far as we know, absence epilepsies are polygenically determined. It is typical of this condition that we have a segregation of clinical seizure types in the descendants of affected individuals.

It may be possible that there is a major gene which is perhaps transmitted and is autosomally dominant, but we have not found it yet.

Question: What is the mode of inheritance in febrile convulsions?

Dr. Doose: There are only a few studies about the

genetics of febrile convulsions, predominantly in Japan, by Fukuyama et al (1979), and Tsuboi (1977), and the study of Frantzen et al (1970) in Denmark. The Danish investigators came to the conclusion that the gene for febrile convulsions may be autosomal dominant. But the Japanese material speaks for a polygenic determination of febrile convulsions. Moreover, it has to be stressed that febrile convulsions are not a homogeneous phenomenon. As we could show in the EEGs of children with febrile convulsions, different genetic factors are involved, including even the rolandic mechanism. So we can say that febrile convulsions are, on the one hand, polygenically determined, and, on the other hand, heterogeneous in origin. In a recent study, Rich et al (1987) came to the same conclusion by complex segregation analysis. However, the authors believed that there could be a subgroup of febrile convulsions transmitted by an autosomal dominant gene.

Question: Do nonepileptic seizure movements have significance? Specifically, are they prognostic in babies with ischemic encephalopathy? What is the prognosis for that group of patients?

Dr. Mizrahi: The prognosis for babies, with hypoxic ischemic encephalopathy is based upon the degree of insult. The occurrence of tonic posturing and motor automatisms is clinical evidence that a significant insult has occurred. The prognosis for these babies is relatively poor.

Question: Are there developmental differences in the kindling thresholds of sites outside the limbic system (specifically, the frontal lobe)?

Dr. Moshé: This has not been studied. Not many people have looked at the frontal cortex to induce seizures. In a preliminary study that we have done, if you give even small amounts of current, you can induce some behavioral manifestations in both age groups. But this may be associated with stimulation of the white matter, which is very easily stimulated with frontal kindling.

Question: Can the possibility be excluded that seizures with no apparent EEG correlation have, in fact, a cortical origin, with low-amplitude, high-frequency epileptiform activity?

Dr. Mizrahi: I cannot exclude the possibility. However, the evidence that these are not epileptic does not depend on the absence of EEG seizure activity, but primarily upon the fact that they behave more like exaggerated brainstem and spinal reflexes.

Question: Have signs of chronic encephalitis ever been seen by Dr. Meencke in cases of generalized epilepsy?

Dr. Meencke: No, we have not seen cases of chronic encephalitis in the definition of Rasmussen. However, we have 68 cases with early onset hemiparesis and epilepsy, and in these, only two cases have signs of chronic encephalitis. It is rarer than what we see in the statistics of Rasmussen of the Montreal group, for example.

Question: Why has hypocalcemia disappeared as an etiology for neonatal seizures? Is it related to a redefinition?

Dr. Mizrahi: I believe that hypocalcemic seizures would be called epileptic in the sense that they are generated by focal cortical hypersynchronous electrical discharges in the brain. Once the metabolic disturbance is corrected, the seizures do not persist.

The reason that hypocalcemia is not seen now very often is due to adjustments in feeding formulas and to increased awareness of the potential for hypocalcemia in stressed infants.

Question: Are the so-called ischemic lesions in infantile spasms really lesions secondary to damage from excitotoxic amino acids?

Dr. Meencke: That is a difficult question, part of which deals with the problem of whether ischemic lesions are the cause or the consequence of seizures. As I have shown in the statistics of these few cases, there is no indication that there is a correlation between grand mal seizures and ischemic lesions, or the duration of hypsarrhythmia and the quantity and quality of ischemic lesions. This would exclude the second explanation: that excitotoxic amino acids would cause these kinds of ischemic lesions.

Question: If morphologic dysgenesis is seen in primary generalized epilepsy, why are these epilepsies age-dependent in expression?

Dr. Meencke: First of all, our studies show that all epileptic syndromes with age-related seizures involve microdysgenesis. The microdysgeneses are the morphological correlates of disturbances during the fetal period. The quality and distribution vary in the different syndromes and probably reflect different manifestation times. The secondary generalized epilepsies involve additional disturbances from different developmental

periods. It is our hypothesis that only fine disturbances of brain development (like diffuse slight microdysgenesis in primary generalized epilepsies) certainly permit late penetrance of the genetic background. On the other hand, severe microdysgenesis or ischemic lesions can be so predominant that the clinical seizure is manifested early and occurs in a form that corresponds with the biodevelopmental degree of maturation of the brain.

Question: What was the gestational age of the infants in Dr. Mizrahi's study?

Dr. Mizrahi: Almost all (85% or more) of the babies in our study were 36 weeks gestational age or greater. In one respect, that is helpful because it provides us with a fairly homogeneous group in terms of gestational age. On the other hand, it gives us only very limited information concerning what actually happens to premature infants.