Letters to the Editor

Am. J. Hum. Genet. 45:977–978, 1989

Brain-Stem Auditory Evoked Potentials in the Fragile X Syndrome

To the Editor:

Some authors have used brain-stem auditory evoked potentials (BAEPs) to study the neurophysiological involvement of the central nervous system in fragile X [fra(X)] subjects (Wisniewski et al. 1985; Ferri et al. 1986, 1987; Gillberg et al. 1986; Arinami et al. 1988), and the results have sometimes been very different.

Wisniewski et al. (1985) reported BAEP findings as normal in six fra(X) subjects; in six of seven autistic fra(X) boys, Gillberg et al. (1986) reported abnormalities, mostly represented by a prolongation of the brain-stem transmission time (I–V interpeak interval).

On the other hand, we have shown, in a group of fra(X) boys, that the latencies are globally delayed, in particular wave III; this causes a lengthening mostly involving the I–III interpeak interval, while the III–V interpeak interval is slightly shortened (Ferri et al. 1986, 1987). One of the possible interpretations of these findings is that fra(X) subjects could present a high-frequency hearing loss, which has already been proved to cause this kind of BAEP abnormalities (Coats and Martin 1977) and could account, at least partially, for speech defects, which are very common in fra(X) subjects.

Moreover, this aspect could also be a sign of delayed maturation of the CNS because, during the first months of life, the I–III interpeak interval changes (shortens) more than the III–V interpeak interval (for review, see Picton et al. 1981); thus, responses recorded a few months after birth resemble, in some way, those recorded in our subjects.

Finally, Arinami et al. (1988) studied BAEPs in a group of 12 fra(X) subjects and found that the III–V interpeak interval is more delayed than I–III, thus suggesting that *central*—as compared with *peripheral*—nervous system dysfunction predominates in these subjects.

It is evident that these results could be viewed as contrasting, but the following considerations are important in understanding the factors causing differences:

1. Studies carried out did not consider other signs of central nervous system involvement, and one of them considered only autistic fra(X) subjects.

2. No correlation has been made with the degree of mental retardation.

3. Groups were sometimes very different in age, our groups (Ferri et al. 1986, 1987) being much younger than that of Arinami et al. (1988): if evolutive aspects are important, then age assumes a critical importance and should be taken into account when discussing results.

4. Diseases affecting the external and middle ear should be screened in order to avoid influences on results because of the high frequency of these kind of diseases (i.e., otitis media) in fra(X) subjects (Hagermann et al. 1987).

5. Therapy and sedation have to be considered because antiepileptic drugs have been shown to cause changes in BAEP latencies (Green et al. 1982*a*, 1982*b*).

In conclusion, the involvement of the brain stem is the common finding in these reports, but it is necessary to carry out more extensive studies, on a larger number

0002-9297/89/4506-0019$02.00

of subjects, to reach a satisfactory understanding of this involvement and of factors influencing it.

RAFFAELE FERRI
Oasi Institute for Research on Mental Retardation and Brain Aging
Troina, Italy

References

Arinami T, Sato M, Nakajima S, Kondo I (1988) Auditory brain-stem responses in the fragile X syndrome. Am J Hum Genet 43:46–51

Coats AC, Martin JL (1977) Human auditory nerve action potentials and brain stem evoked responses. Arch Otolaryngol 103:605–622

Ferri R, Bergonzi P, Colognola RM, Musumeci SA, Sanfilippo S, Tomassetti P, Viglianesi A, et al (1986) Brainstem auditory evoked potentials in subjects with mental retardation and different karyotypes. In: Gallai V (ed) Maturation of the CNS and evoked potentials. Elsevier, Amsterdam, pp 369–374

Ferri R, Colognola RM, Falsone S, Musumeci SA, Petrella MA, Sanfilippo S, Viglianesi A, et al (1987) Brainstem auditory and visual evoked potentials in subjects with fragile-X mental retardation syndrome. In: Barber C, Blum T (eds) Evoked potentials III. The third international evoked potentials symposium. Butterworths, London, pp 167–169

Gillberg C, Persson E, Wahlström J (1986) The autism-fragile-X (AFRAX): a population-based study of ten boys. J Ment Defic Res 30:27–29

Green JB, Walcoff MR, Lucke JF (1982*a*) Comparison of phenytoin and phenobarbital effects on far-field auditory and somatosensory evoked potential interpeak latencies. Epilepsia 23:417–421

——— (1982*b*) Phenytoin prolongs far-field somatosensory and auditory evoked potentials interpeak latencies. Neurology 32:85–88

Hagermann RJ, Altshul-Stark D, McBogg P (1987) Recurrent otitis media in the fragile X syndrome. Am J Dis Child 141:184–187

Picton TW, Stapells DR, Campbell KB (1981) Auditory evoked potentials from the human cochlea and brainstem. J Otolaryngol 10(Suppl 9): 1–41

Wisniewski KE, French JH, Fernando S, Brown WT, Jenkins EC, Friedman E, Hill AL, et al (1985) Fragile X syndrome: associated neurological abnormalities and developmental disabilities. Ann Neurol 18:665–669

Am. J. Hum. Genet. 45:978–979, 1989

Reply to Dr. Ferri

To the Editor:

I am grateful to Dr. Ferri for his comment on our paper (Arinami et al. 1988) and especially for his calling my attention to the developmental aspect of auditory brainstem responses (ABRs) in the fra(X) syndrome. I feel a great interest in the result of ABRs in eight fra(X) mentally retarded boys (average age 13.8 years) shown by Dr. Ferri et al. (1986), lengthening of the I–III interpeak interval, which appears opposite to ours, prolonged III–V interval. Though I have no definite answer to what caused these differences, the difference in age between the two groups seems one of the causes, as Dr. Ferri pointed out. In our fra(X) subjects (average age 32 years), the correlation coefficients of age with the I–III interval and with the III–V interval were −.25 and .49, respectively, while this difference between the coefficients of the two intervals was not seen in the control group. These correlations are not statistically significant, but they imply that the results of both studies might not be inconsistent with each other.

Dr. Ferri hypothesized that lengthening of I–III intervals is a sign of delayed maturation of the central nervous system in the fra(X) patients. On the other hand (Lachiewicz et al. 1987) has suggested decline in IQ among fra(X) males. Lengthening of III–V interval with increasing age might be a sign of the degenerative nature in the central nervous system function of the fra(X) patients. I admit these developmental or degenerative explanations seem too simple, because ABR changes correlating with the ages of the individuals examined by Dr. Ferri et al. and by us are thought to be small in the general population (Beagley and Sheldrake 1978), especially when these changes are recorded at the higher stimulus intensities that we used. Only further extensive studies will answer these questions. In any case, I think these developmental considerations are compatible with our anatomical ones, discussed in our paper.

I agree with Dr. Ferri that there are many factors causing differences in ABRs and that such factors must be thoroughly considered when one does experiments and interprets the results. Some are the factors related to the fra(X) which are important in more comprehensively understanding the disease, and the others are the ones not related with the fra(X), which therefore lead to misunderstanding. Here, I would like to take brief