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Differential rates of age of seizure onset between sexes and between hemispheres?

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Abstract

In a *descriptive* analysis of 158 patients with temporal lobe epilepsy, Taylor (1969) reported that the age of first seizure varied systematically as a function of laterality and sex. We conducted *inferential* analyses of Taylor's original data which (1) provided support for his proposal of disproportionate left hemisphere vulnerability to seizure onset in early life, but (2) failed to provide evidence of sex differences in age of onset of unilateral seizures. Examination of these effects in a larger sample of 844 patients drawn from the Bozeman Epilepsy Consortium provided some additional support for findings from the inferential analysis. Specifically, the left hemisphere appeared more vulnerable to seizure onset in childhood, this increased vulnerability extending to about age 5 years. Age of onset of seizures was not different when males and females were compared. Thus, reanalysis of Taylor's original data as well as examination of data from a larger, more contemporary sample suggest that seizure onset varies as a function of laterality, but not sex. (*JINS*, 1997, *3*, 428–434.)

Keywords: Laterality, Sex, Age of seizure onset, Epilepsy

INTRODUCTION

Taylor (1969), studying 158 patients with temporal lobe epilepsy, reported that the age of first seizure varied as a function of lesion laterality and sex. During the 1st year of life, epilepsy was more than twice as likely to be of left as opposed to right hemisphere origin. This increased left hemisphere vulnerability was not observed after this period. Further, in males, the inception rate fell away smoothly with increasing age, whereas in females, the fall appeared to be much sharper and occurred mainly in the 2nd year of life. The findings were hypothesized to stem from differential rates of maturation between the hemispheres and sexes, presumably due to the effects of at least two genetic factors, each with its own age-dependent pattern of manifestation. With regard to hemispheric vulnerability, Taylor suggested that the functional maturation of the left hemisphere lags behind the right and therefore is at greater risk to cerebral damage early in development. To explain the sex-related differences, Taylor argued that maturation proceeds more slowly in males than in females, so that boys are at risk for a longer time.

It is important to note that Taylor's novel hypotheses raise questions for a number of reasons. First, the study sample was composed of two groups that varied in the certainty with which the diagnosis of unilateral seizure onset could be ascertained. Sixty-five cases of medial temporal sclerosis were drawn from the Guy's-Maudsley neurosurgical unit and had undergone temporal lobectomy for the relief of temporal lobe epilepsy. In contrast to such unequivocal cases of unilateral seizure onset, 100 additional children were taken

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from Ounsted et al. (1966) and "differed from the Guy's-Maudsley series in age at ascertainment, source, and clinical purpose.... In this series, 65 patients had largely or exclusively lateralized foci in the electroencephalogram (Taylor 1969, p. 141)." Second, his data were presented as graphs of raw frequencies rather than as proportions. As a result, the graphs may be difficult to interpret, because the comparison groups differed in sample size (e.g., in the case of sex, there were 90 males and 68 females). For example, 45 cases out of 90 carries a different meaning than 45 cases out of 68. A more appropriate approach to compare the genders requires converting the raw frequencies to relative frequencies, a procedure that results in a common metric, and in fact underlies any inferential comparison between the groups. Further, Taylor did not conduct statistical analyses, but rather relied on descriptive methods. Accordingly, *the first goal* of the current study was to carry out an inferential analysis of Taylor's original data set.

Despite these concerns, there is some evidence to support Taylor's proposal that the left hemisphere develops at a slower rate than that of the right and is disproportionately vulnerable to early cerebral damage. For example, the sylvian fissure appears chronologically earlier in the right hemisphere (Chi et al., 1977) and higher order dendritic branching in anterior regions first appears in the right hemisphere (Scheibel, 1984). With regard to differential hemispheric vulnerability, there are reports of a relative increase in right-sided infantile and childhood hemiplegia (e.g., Annett, 1973; Levine et al., 1987) and a greater sensitivity of the left hemisphere to perinatal insult (Raz et al., 1994a). The limits of the maturational period during which cerebral lesions are more likely to affect the left hemisphere, however, remain to be established.

Consistent with the notion of delayed maturation in males, there is evidence that beginning with gestation, males are more vulnerable to adversity than females. There is a higher frequency of miscarried and stillborn males and the risks for adverse obstetric and neonatal complications are elevated in males (see Raz et al., 1994b, for a recent review). Similarly, whether incidence of first afebrile seizure or epilepsy are considered, rates are slightly higher among males than among females. Although there is some inconsistency among studies, on average, the incidence of first seizure or epilepsy is between 1.1 and 1.7 times greater in males than in females (see Hauser & Hesdorffer, 1990, for review). Similarly, most (though not all) studies report that the prevalence of active epilepsy is higher among males than among females. In those studies that report an increased prevalence among males, rates ranged from 1.1. to 3.3 times that among females (see Hauser & Hesdorffer, 1990, for review). Although there is substantial evidence to support sex differences in early vulnerability, the window of time during which males are more vulnerable than females has not yet been defined.

Accordingly, *the second goal* of this study was to examine the relations among age at seizure onset, hemisphere of seizure origin, and sex in a large and contemporary sample. Regarding Taylor's hypotheses, we expected to find an increased vulnerability to the left hemisphere in early developmental epochs, and also anticipated that the inception rates would differ between the sexes, with females showing a sharp decline in vulnerability early in childhood.

We expanded on previous studies in the following ways. First, our pool of participants represents the largest group of patients with epilepsy (most with temporal lobe epilepsy) studied to date and comes from the Bozeman Epilepsy Consortium, a collaboration among eight epilepsy surgery centers in the United States and Canada. Second, log linear analysis was used to compare the distribution of age of seizure onset between males and females, and between individuals with left- *versus* right-sided foci. Two types of log linear models were fitted to the data. The first was an omnibus model that treated all variables as categorical, and evaluated whether the distribution of age of seizure onset varied by gender or by focus in any way. The second model treated age of seizure onset as an ordinal variable, and tested the more focused question of whether the gradients (that is, the linear trend) across age of seizure onset differed between the genders, and between foci (Agresti, 1984).[1] In this way, the boundaries of any age-dependent patterns could be more clearly delineated.

STUDY 1: REANALYSIS OF TAYLOR'S DATA

As indicated earlier, Taylor's original data were reported as raw frequencies (see Figures 1 and 2). Such a presentation can be problematic when cell sizes differ, as in the case for sex. The data for sex are represented, using percentages, in Figure 3. Comparison of the graphs (frequency *vs.* percentage) reveals evident differences. Visual inspection of the frequency graph (Figure 2) suggests a rather large difference between males and females at about 2 years of age. This apparent sex effect shrinks, however, when the graph displaying percentages is examined. With regard to hemispheric effects, two graphs (frequency *vs.* percentage) are not necessary because there were an equal number of cases with left- *versus* right-sided foci.

Because Taylor did not analyze his data by means of inferential statistical techniques, we reevaluated his data using log linear analysis, initially with all variables treated as categorical, and then with seizure onset treated as an ordinal variable.

With regard to laterality of focus (see Figure 1), Taylor reported that "left sided lesions were common in the first year and rare after two years, while right-sided lesions were equally prevalent in those illnesses which first presented during the first four years of life (p. 140)." When we examined Taylor's data for the relation between seizure onset and

[1]Note that it is possible for an omnibus test to be nonsignificant while the test for the linear trend is significant. This situation is similar to ANOVA models where significant trends can occur in the presence of nonsignificant omnibus tests.

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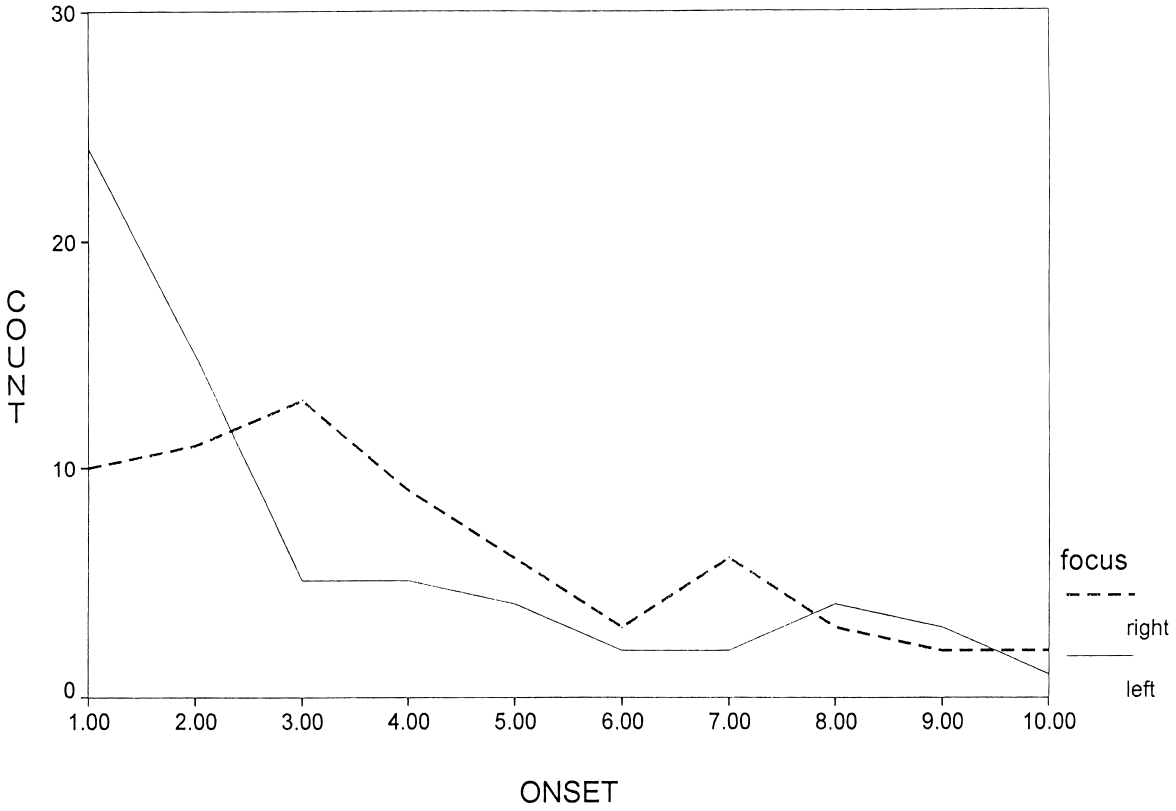

Fig. 1. Taylor's focus by onset data: Raw frequencies.

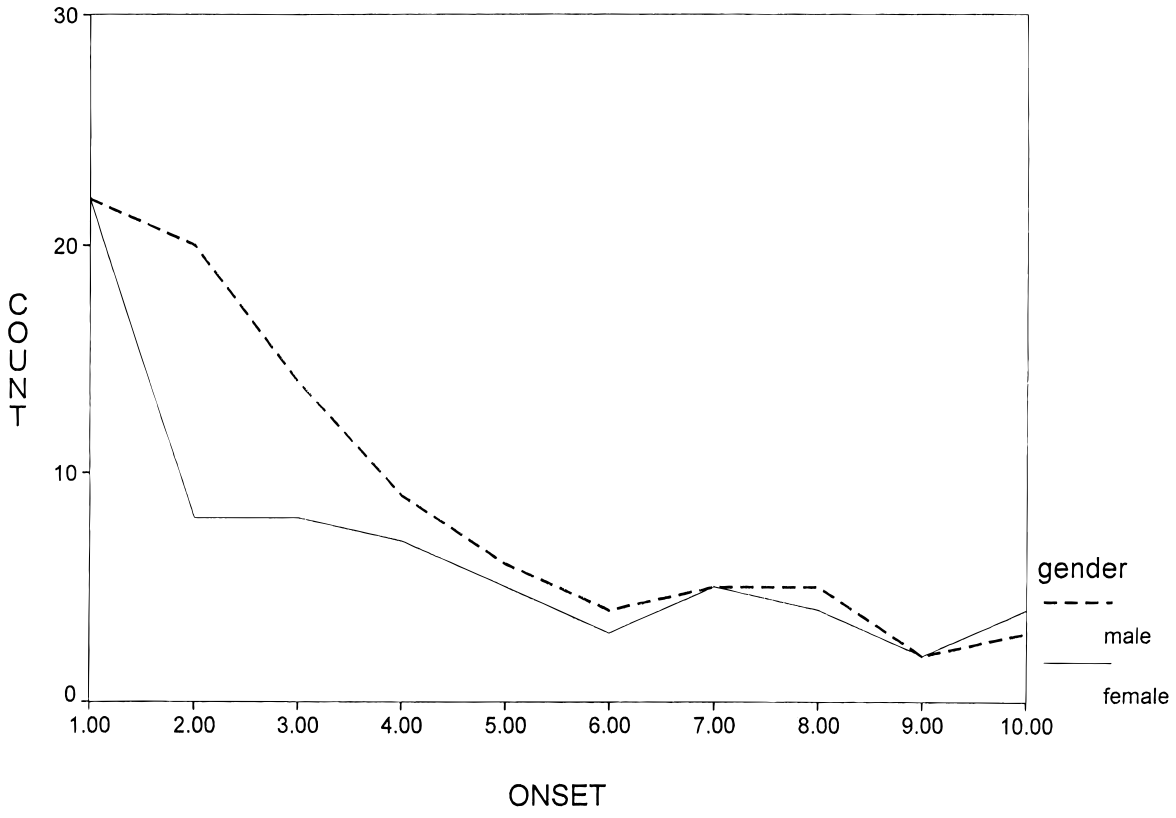

Fig. 2. Taylor's sex by onset data: Raw frequencies.

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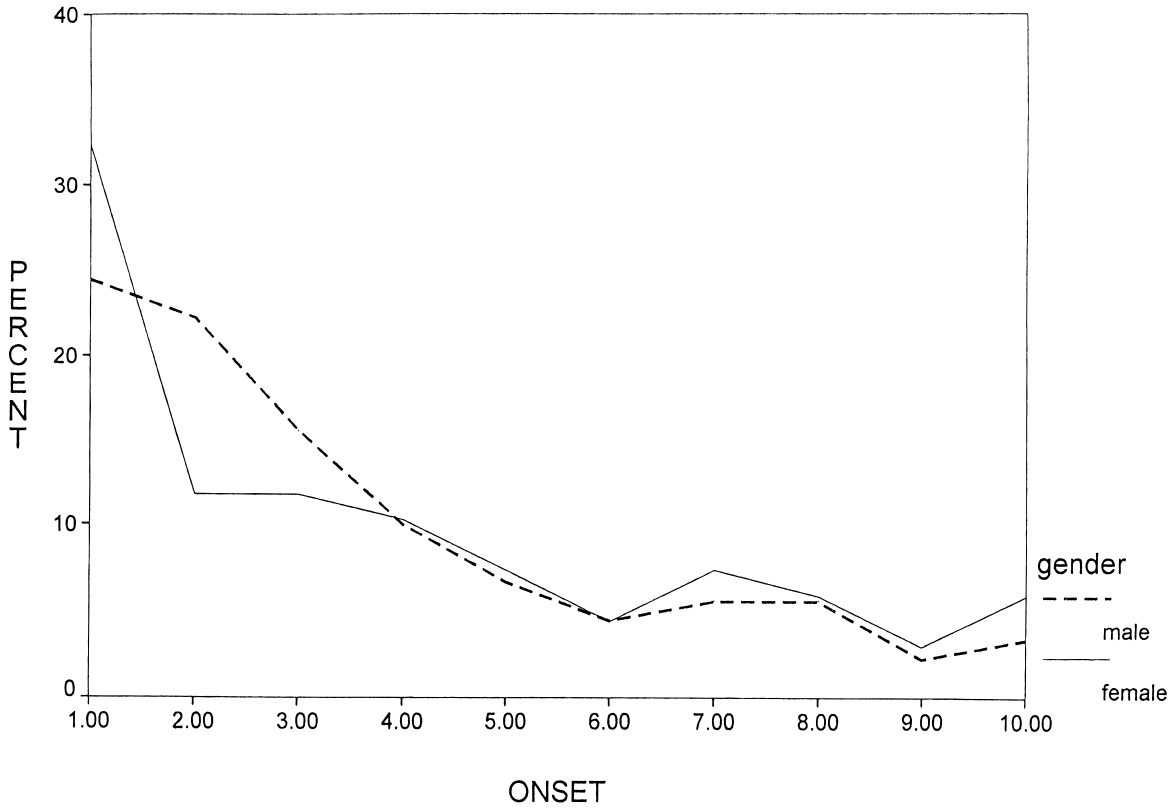

Fig. 3. Taylor's sex by onset data: Percent.

focus (see Figure 1), the omnibus test approached significance [$\chi^2(9) = 16.33$, $p < .06$], indicating that overall, the distribution of age of seizure onset differed between individuals with left- *versus* right-sided foci.[2] When age of seizure onset was treated as an ordinal variable, we found the two gradients to differ [$\chi^2(1) = 5.94$, $p < .025$], in agreement with Taylor's interpretation, although the overall gradient difference is due mainly to the increased risk to the left hemisphere within the first year of life [$\chi^2(1) = 6.55$, $p < .025$]. In contrast to Taylor, the two hemispheres do not differ statistically with regard to risk after this period ($p > .05$ for all subsequent years).

Turning to the relation between seizure onset and gender, Taylor suggested that the gradients for seizure onset differed between the sexes: "For males the decline is smooth over the first four years whereas for females the decline is much more sharp, occurring mainly in the second year of life (p. 141)." Our reanalysis of Taylor's data did not reveal any statistically significant sex-related differences either overall [$\chi^2(9) = 4.54$, $p > .05$], or when the linear component of seizure onset was analyzed [$\chi^2(1) = .37$, $p > .05$].

[2]Note that in the omnibus test, this analysis compares proportions across age, which is divided into 10 categories. Accordingly, there are 9 degrees of freedom in the chi square. When age of seizure onset is treated as an ordinal variable, it evaluates the linear trend across epochs which is a single degree of freedom test.

STUDY 2: DATA FROM THE BOZEMAN EPILEPSY CONSORTIUM

Given the dearth of studies in this area, and the provocative nature of his hypotheses, we examined the relations among age at seizure onset, hemispheric vulnerability, and sex in a very large and contemporary sample of patients. Because Taylor evaluated these effects only when age of onset was in the first decade, our initial analysis focused on that time frame, but we also examined them from birth to adulthood in order to identify any age-related changes across the life span.

Research Participants

Participants were patients with medically refractory seizures from the Bozeman Epilepsy Consortium, a collaboration among eight epilepsy surgery centers (Cleveland Clinic, Long Island Jewish Medical Center, Mayo Clinic, Epi-Care Center, Yale University, New York University/Hospital for Joint Diseases, Medical College of Georgia, and University of British Columbia (and University of Victoria). The current data base consists of more than 1500 patients, most with temporal lobe epilepsy, who have been evaluated for possible surgical treatment. The data collection took place over approximately the past 10 years. These patients were evaluated intensively at all institutions to the

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degree that each institution was convinced that evidence regarding lateralization was certain enough to recommend surgery. Diagnostic procedures, at a minimum, included monitoring of spontaneous seizures at all institutions (with varying degrees of invasiveness) and neuroimaging. Patients were considered for inclusion in this study if they met the following criteria: (1) neurophysiological evidence of complex partial seizure onset from either the right or the left hemisphere, (2) information was available regarding age at onset of recurrent seizures and gender, and (3) no neuroradiological evidence of lesions other than mesial temporal sclerosis.

Our final sample consisted of 844 individuals, 426 males (50.5%) and 418 (49.5%) females. The seizure origin was right-sided in 388 patients (46%) and left-sided in 456 (54%). Most of the patients (93.2%) had temporal lobe dysfunction. Preliminary analyses revealed that those with extratemporal disturbances showed the same pattern of results as those with temporal lobe dysfunction. Accordingly, the results of the combined sample are reported here. The mean age of the sample was 30.91 years ($SD = 10.06$). In general, age of onset of recurrent seizures (referred to here as seizure onset) was in childhood (11.18 years, $SD = 9.95$). The seizure onset data were categorized in yearly intervals until age 10 years, in 2-year intervals until age 20 years, 5-year intervals until age 50 years, after which the remaining data were combined into one final group. The rationale underlying this categorization was to avoid sparse and empty cells in data analysis. The recategorized data are shown in Figures 4 and 5.

RESULTS

Birth to 10 Years

These analyses focused on the time frame used in Taylor's study. For these analyses, the sample consisted of 423 individuals (178 with right-sided foci, 245 with left-sided foci; 205 males, 218 females). Most (93.1%) had temporal lobe dysfunction. The mean age of the sample was 28.27 years ($SD = 9.49$). Seizure onset was in early childhood (3.41 years, $SD = 2.60$). The data are shown in Figures 4 and 5 (those points up until age 10 years).

Loglinear analysis of the focus by age of seizure onset data revealed no significant relation either overall [$\chi^2(9) = 11.91$, $p = .22$] or when seizure onset was treated as an ordinal variable [$\chi^2(1) = 1.54$, $p = .21$]. Similarly, the relation between sex and seizure onset was nonsignificant overall [$\chi^2(9) = 4.49$, $p = .88$] and when seizure onset was considered an ordinal variable [$\chi^2(1) = .79$, $p = .38$].

Birth to Adulthood

For these analyses, the entire sample ($n = 844$) was included (see Research Participants). Loglinear analysis of the focus by seizure onset data revealed a significant over-

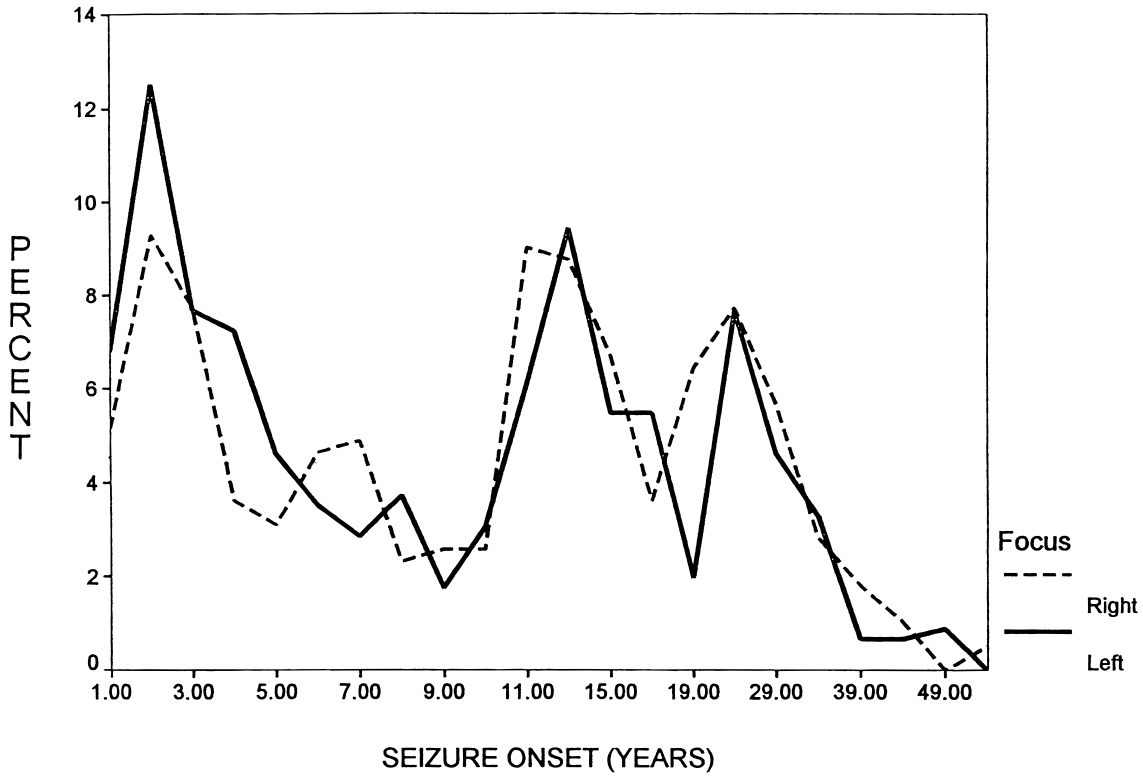

Fig. 4. Focus and seizure onset.

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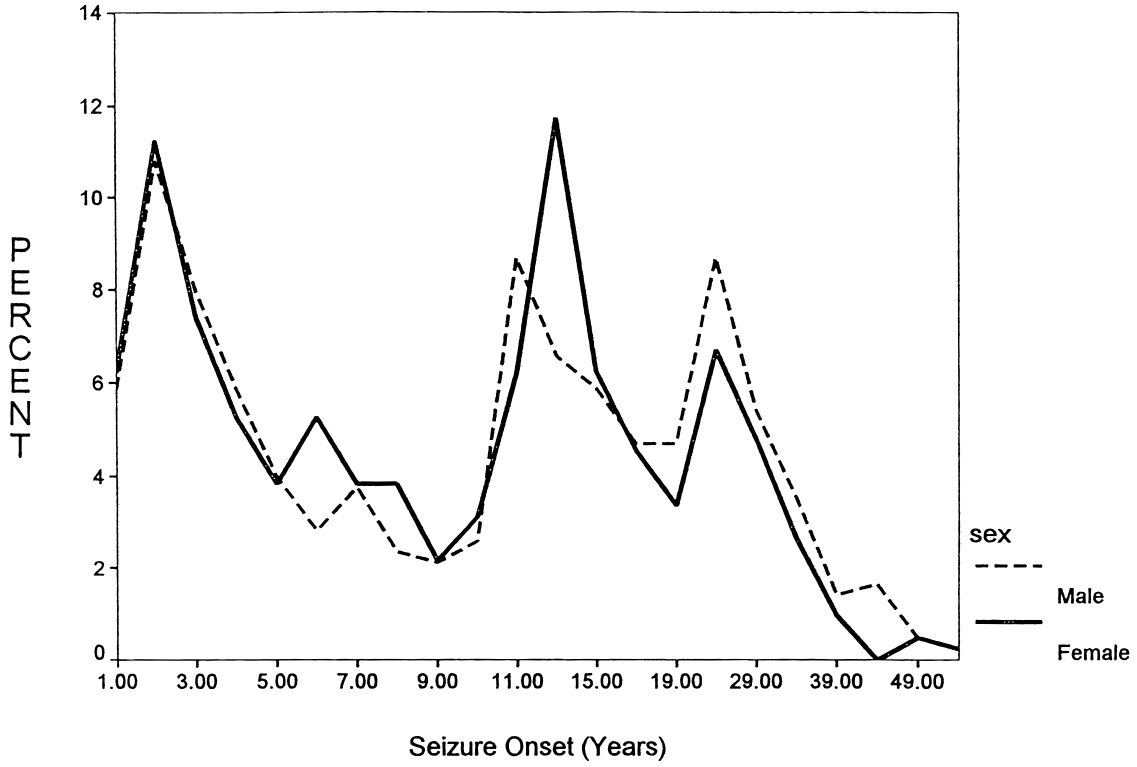

Fig. 5. Sex and seizure onset.

all relation [$\chi^2(21) = 38.25$, $p = .01$]. There was also a significant trend across age of onset indicating that left-sided seizures were more common early in life, this increased vulnerability decreasing with increasing age [$\chi^2(1) = 5.98$, $p < .02$]. Inspection of Figure 4 suggests that in contrast to Taylor's proposal, the left hemisphere vulnerability persists past the 1st year of life and extends into childhood. After about age 5 years, this left hemisphere vulnerability diminishes, with the incidence of left-sided seizures matching that of right-sided ones [$\chi^2(1) = 6.90$, $p < .001$, Cramer's V = .09]. Put another way, an individual is about 1.45 times more likely to have a left-sided seizure origin in early childhood than after 5 years of age.

Loglinear analysis of the sex by seizure onset data revealed no significant overall relation [$\chi^2(21) = 23.03$, $p = .34$], nor was there a trend across age of onset [$\chi^2(1) = 1.88$, $p = .17$].

COMMENT

Reanalysis of Taylor's (1969) data, using inferential techniques, provided some support for his proposal of disproportionate left hemisphere vulnerability early in life, but failed to find evidence of sex differences in age at onset of unilateral seizures. Convergent evidence for these results comes from findings from our large data base, which has taken more than a decade to accumulate across multiple centers, which themselves are variable in evaluation procedures. If anything, the findings with regard to laterality are probably conservative, in that they have emerged over considerable background noise. It is conceivable, however, that missing data (e.g., etiology, racial composition) and variability in diagnostic methods could mask a small sex effect.

Our findings with regard to hemispheric differences are only partly consistent with Taylor's data, although in fairness, the range of seizure onset was restricted in his data set to early childhood, prior to age 10 years; his sample size was considerably smaller; he examined age at first seizure, not age of onset of recurrent seizures; and the methods of evaluation of patients have changed dramatically over the years. In contrast to Taylor's proposal, we found that the left hemisphere vulnerability persists past the 1st year of life and extends until about age 5 years. Nonetheless, the data are broadly compatible with his model of a right-to-left maturational gradient, in which the less mature hemisphere is the more vulnerable.

One might question why the overall analysis (birth to adulthood) found a significant laterality effect, whereas the analysis that focused on birth to age 10 years did not. This is unlikely to reflect merely a difference in sample size (423 *vs.* 844) since the ratio of participants to age epochs is similar in both analyses. Rather, the laterality effect becomes evident only in the context of the entire age range. It is worth noting that right hemisphere foci were not more common than left-sided ones at older ages. With seizure onset after age 10 years, half of the sample had right-sided foci ($n = 210$ or 50%) and half had left-sided seizure origin ($n = 211$ or 50%).

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Taylor's proposal for a second genetic factor, contributing to sex-related differences in seizure onset, was not supported either when his own data were reanalyzed or in our data. There are sex differences in incidence of epilepsy, but they do not appear to reflect developmental processes that interact with age.

Several important questions remain to be answered. Our sample is limited to those with severe seizure disorder. Would different results obtain in a broader sample—at least for sex differences? What are the mechanisms that account for the differential hemispheric pattern of vulnerability to seizure onset early in development? Does the decreased vulnerability of the right hemisphere early in life really reflect increased maturation? Is this pattern of vulnerability attributable to specific types of neurological conditions? What are the cognitive consequences (advantages?) of such a differential pattern of vulnerability? In a purely speculative vein, the greater maturity of the right hemisphere during early development may enhance its resilience to the adverse consequences of early cerebral insult. Do the same effects occur in nonhuman primates? We hope that the advent of *in vivo* neuroimaging techniques and the increased collaboration among research centers may permit some of these questions to be addressed.

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