

Effects of Age of Onset of Tonic-Clonic Seizures on Neuropsychological Performance in Children

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Summary: Forty-eight children (aged 9 to 15 years) with tonic-clonic seizures were administered a neuropsychological test battery. The children with seizures of early onset (before age 5) were significantly impaired relative to the children with later onset on 8 of the 14 measures in the battery. The deficits were seen on tasks whose requirements included the repetition of a simple motor act, attention and concentration, memory, and complex problem solving. These findings emphasize the need for further research to determine the causal factors of the greater dysfunction seen in the early onset group.

The age at which brain damage is sustained appears to be an important determinant of the nature and extent of subsequent behavioral deficits (Teuber and Rudel, 1962; Fitzhugh and Fitzhugh, 1965; Boll, 1973). A number of studies have explored the related issue of the behavioral sequels of early versus later onset of seizure disorders (Collins, 1951; Rodin, 1968; Kløve and Matthews, 1969; Dikmen et al., 1975, 1977). These studies have found that persons with early onset of seizures generally perform more poorly on psychometric measures of intelligence than do persons whose seizures begin later in life. Adequate evaluation of the effects of age of onset is difficult to achieve, however, because of the many factors which have been demonstrated to affect performance in persons with

epilepsy. A partial listing of such factors include variables specific to epilepsy such as seizure type (Fedio and Mirsky, 1969; Glowinski, 1973), site of epileptic focus (Cherlow and Serafetindes, 1976; Dennerill, 1964), and etiology (Matthews and Kløve, 1967) as well as more general variables known to affect performance, such as educational level, age at time of testing, and socioeconomic status. Additionally, both duration of seizure disorder (and therefore absolute number of seizures) and the duration of usage of antiepileptic drugs covary with age of onset. It is extremely difficult, therefore, to isolate the effects of age of onset from the combined effects of the many confounding variables which have been shown to affect performance.

The present study represents an attempt

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to give additional information concerning the effects of age of onset by controlling as many relevant variables as possible. The availability of a large group of patients who had received neuropsychological evaluation at the Highlands Center, Comprehensive Epilepsy Program, in Charlottesville, Virginia, allowed the selection of early and late onset groups which were well matched on variables such as education, socioeconomic status and prescribed antiepileptic medication. Only patients whose predominant seizure type was tonic-clonic were included in the study. Duration effects were controlled by statistical means (analysis of covariance) rather than by attempting to establish early and late onset groups which had equivalent seizure durations. This statistical approach had the advantage of allowing for the testing of subjects in early and late onset groups at equivalent ages.

An additional purpose of the present study was to give information concerning the effects of age of onset on performance in patients in their school years, a time in which the effects of cognitive dysfunction may be particularly devastating. Previous studies of the effects of age of onset have for the most part utilized adult patients with chronic seizure disorders. There is evidence that different patterns of intellectual functioning may be seen in persons with acute as opposed to chronic seizure disorders (Kløve and Fitzhugh, 1962; Fitzhugh et al., 1962). The testing of subjects at young ages (9–15 years) relatively close to the age of seizure onset could reveal patterns of deficit which would not be evident in older adults who have seizure disorders of long standing.

METHOD

Subjects

Forty-eight subjects (28 males and 20 females) were selected from a large group of patients examined. All patients included in the study had been classified by a

neurologist on the basis of all available medical information as having tonic-clonic seizures as their primary seizure type, based on the International Classification (Gastaut, 1970). Additional criteria for inclusion in the study were an age at time of testing of between 108 and 179 months (this corresponds to the age range of the Halstead Neuropsychological Test Battery for Children) and a full scale IQ of 60 or greater. All patients tested at the Highlands Center who met these criteria were included in the study.

The median age of onset of the 48 subjects selected for the study was 60 months and an early and a later onset group was constructed by dividing the subjects at this median. This resulted in an early onset group of 24 subjects (13 males, 11 females) who ranged from 1–60 months in age of onset, and a later onset group of 24 subjects (15 males, 9 females) who ranged from 60–170 months in age of onset. Table 1 gives descriptive neurological and demographic information for the two groups.

Patients in the early onset group whose first seizure was febrile all had several other tonic-clonic seizures occurring before the age of 60 months. Seizures were well controlled in both early and late onset groups and no subjects in either group had had a seizure in the month preceding testing. Seizure frequency in the year preceding testing was somewhat higher in the late onset group with 10 subjects having had one or more seizures in the past year in the late onset group as opposed to three subjects in the early onset group.

Tests

The Halstead Neuropsychological Test Battery for Children and Allied Procedures were administered to all subjects by trained psychology technicians. The tasks are similar to the adult battery used by Dikmen et al. (1975, 1977) but are modified somewhat to allow administration to younger subjects. A full description of the children's battery

TABLE 1. Descriptive information for groups with early (0–60 months) and late (61–170 months) age of seizure onset

Parameter	Early (n = 24)	Late (n = 24)
Age ^a		
\bar{X}	145.9	154.6
(SD)	(20.4)	(22.1)
Education ^b		
\bar{X}	5.2	5.9
(SD)	(1.6)	(1.7)
SES		
\bar{X} ^c	64.1	61.2
(SD)	(10.5)	(15.9)
Onset ^a		
\bar{X}	28.5	101.9
(SD)	(19.5)	(31.2)
Duration ^a		
\bar{X}	114.8	53.7
(SD)	(35.7)	(26.3)
Etiology		
Unknown	14	22
Febrile	6	0
Perinatal or birth trauma	2	1
Encephalitis	1	0
Trauma	0	1
Drugs		
Phenobarbital	12	10
Phenytoin	9	14
Other	3	0

^a Age, onset and duration are in months.

^b Education is in years completed; one child in the early and two in the late onset groups were in special education classes and were not used in computing the means.

^c SES—socioeconomic status—is computed as in Hollingshead (1957); higher scores indicate lower SES.

is available elsewhere (Boll, in press; Reitan and Davinson, 1974) but a brief description of each task will be given here for convenience and to allow comparison with the adult battery.

The Wechsler Intelligence Scale for Children—Revised (WISC-R) offers a standard psychometric measure of intelligence.

The Halstead Category Test (Categories) requires the subject to discover an underlying concept in order to correctly classify a series of items projected one at a time on a screen. The score is the number of errors made on 168 items distributed into six separate tests (the adult version contains 208 items and seven subtests).

Tactual Performance Test (TPT) requires the subject, while blindfolded, to place six blocks in their proper positions on a formboard (the adult version has 10 blocks). The task is performed first with the dominant hand, then with the nondominant hand, and finally with both hands together. While it is possible to derive a number of different scores, the values to be reported here represent an average over all trials of the time necessary to place one block (*TPT-time*). After completing the formboard, the subject is unexpectedly asked to draw the blocks in their proper spatial location. This yields two scores: the number of blocks whose shapes are correctly recalled (*TPT-memory*), and the number of blocks whose locations are correctly recalled (*TPT-location*).

Trail Making Test, Parts A & B (Trails A & B). Part A requires the subject to sequentially connect 15 numbered circles. Part B requires alternation between numbers and letters in connecting labeled circles, e.g., from circle 1 to circle A to circle 2 to circle B. Trails A and B both have 15 circles (the adult version has 25 circles for each part).

The Speech Sounds Perception Test (Speech) requires the discrimination of nonsense words presented on a tape recorder and the choice of the correct option from three printed alternatives (the adult version has four alternatives). There are 60 items with the score being the number of errors. The *Rhythm* and *Tonal Memory* measures are two subtests of the Seashore Test of Musical Ability which require, respectively, the discrimination of differences in sequences of rhythms or tones. Both utilize number correct as the score. The Rhythm test is identical to that given in the adult battery. Tonal memory is not a standard part of either the children's or the adult battery.

The Finger Oscillation Test (Tapping) measures speed of tapping with the dominant index finger. The *Strength of Grip Test (Grip)* measures gripstrength (in kilograms)

of the dominant hand with a plunger type dynamometer. Both tapping and grip are identical to the tests administered to adults. One final difference between the adult and the children's midrange battery is that no impairment index (a summary measure) is computed for children.

RESULTS

The data from each task were separately submitted to a one-way analysis of covariance with onset (early vs. late) as the independent variable and duration as the covariate. *The Statistical Package for the Social Sciences* subprogram ANOVA, which uses regression procedures to remove variation in the dependent variable due to the covariate, was utilized for each analysis.

Table 2 lists the means and standard deviations for each task as well as the means for each task when the effect of duration is covaried out. On eight measures, the early onset group performed significantly more poorly than did the late onset group. These measures are: WISC-R Full Scale IQ, Categories, TPT-location, Trails A and Trails B, Tonal-Memory, Speech, and Tapping. The remaining six measures also indicated inferior performance by the early onset group though the differences were not statistically significant.

Table 3 lists the subtest scores from the WISC-R. Again, all 10 measures are in the direction of superior performance by the later onset group, although only three measures showed significant differences. These were the Comprehension, Vocabulary, and Picture Completion subtests.

The analysis of covariance yields *F* ratios for the covariate (duration) as well as for the independent variable (onset). In only one instance was duration significant. This was for the Picture Completion subtest of the WISC-R. As expected, the overall correlation between onset and duration was highly significant, $R = -0.80$, $p < 0.005$.

DISCUSSION

The data from the present study support the conclusion that children who begin to have tonic-clonic seizures at an early age are impaired relative to those with later onset on a number of measures of intellectual and adaptive ability. An important aspect of the present findings is the fact that the deleterious effects of an early age of onset can be seen at a young age, while the child is still undergoing growth and development. Further, the effects are seen on a variety of tasks which require very different abilities. Inspection of Table 2 indicates that the early onset group performed significantly more poorly than did the late onset group on 8 of the 14 tests in the battery. The deficits were seen across a broad range of tasks whose requirements included the repetition of a simple motor act, attention and concentration, memory, and complex problem solving. Thus, tonic-clonic seizures which begin before the age of five years appear to result in a lowering of functioning across a wide spectrum of human abilities, simple as well as complex.

The finding that an early age of seizure onset is more harmful to intellectual ability than is later onset would appear, at first glance, to be in conflict with the widely accepted principle that the brain is more "plastic" early in development and is, therefore, better able to compensate for early versus later damage. Evidence using human subjects which supports the plasticity argument comes largely from studies of recovery of function in children and adults following cortical damage (e.g., Basser, 1962; Kohn and Dennis, 1974; Lenneberg, 1967; Teuber and Rudel, 1962). While there have been questions in recent years concerning conclusions drawn from these data which relate to the issue of the development of cerebral dominance (Kinsbourne, 1976; O'Leary, in press), the basic concept that the nervous system is more plastic early in development has been widely supported

TABLE 2. Raw score means and standard deviations, means adjusted for covariate (duration) and F ratios for early and late onset groups on each test

Test	Early onset		Late onset		F-ratio
	Mean raw score (and SDs)	Mean adjusted for duration	Mean raw score (and SDs)	Mean adjusted for duration	
VIQ	82.9 (12.9)	81.2	89.2 (13.1)	90.9	3.31
PIQ	79.9 (13.9)	79.9	91.5 (15.4)	91.5	3.64
FSIQ	80.0 (12.1)	79.0	89.4 (13.8)	90.4	4.54 ^a
Categories	54.8 ^d (20.9)	63.85	49.3 (23.9)	39.3	8.10 ^b
TPT-time	47.1 ^e (43.5)	54.2	36.4 (31.4)	28.9	2.63
TPT-memory	3.8 ^f (1.4)	3.9	4.3 (1.3)	4.4	0.90
TPT-location	1.9 ^g (1.8)	1.6	3.3 (1.5)	3.6	8.50 ^b
Trails A	27.0 ^h (16.4)	30.9	15.4 (5.8)	11.4	15.9 ^c
Trails B	52.1 ^h (35.6)	61.0	31.4 (13.0)	22.1	13.4 ^c
Tonal-memory	11.6 ⁱ (4.7)	9.9	14.0 (6.4)	15.8	7.0 ^b
Rhythm	21.9 ⁱ (4.4)	21.0	22.0 (6.4)	22.1	0.81
Speech	12.7 ^g (9.3)	14.2	10.3 (5.8)	7.7	5.0 ^a
Grip (dominant hand)	20.6 ^j (7.5)	19.4	23.3 (6.3)	24.5	3.15
Tapping (dominant hand)	33.9 ^k (10.8)	30.7	36.6 (11.4)	39.9	4.4 ^a

^a $p < 0.05$.^b $p < 0.02$.^c $p < 0.001$.^d No. of errors.^e Seconds per block.^f Number of blocks correctly recalled.^g Number of blocks correctly located.^h Seconds to complete.ⁱ No. correct.^j In kilograms.^k No. of taps in 10 sec.

(see Whitaker, 1976 for a review). The effects of age of onset of brain injury in general, and of tonic-clonic seizures in particular, must, however, be considered in the context of several other important factors as well as plasticity. A number of authors (Boll and Barth, in press; Dreifuss, 1975; Kinsbourne, 1974), have pointed out the importance of the location, focal spe-

cificity, extent, and permanence of the damaged area in determining the nature of behavioral deficits following brain injury. A factor of central importance to the issue of effects of seizure onset is the continuing presence of an impaired but nonsilent brain area. The fact that the site of the impaired tissue is probably subcortical in persons with tonic-clonic seizures (Penfield and

TABLE 3. Raw score means and standard deviations, means adjusted for covariate (duration) and F ratios for subscales of WISC-R

Test	Early onset		Late onset		F-ratio
	Mean raw score (and SD)	Mean adjusted for duration	Mean raw score (and SD)	Mean adjusted for duration	
INFO	6.5 (2.7)	6.8	7.7 (2.6)	7.4	0.36
COMP	7.7 (2.2)	7.0	8.6 (2.0)	9.2	67.60 ^a
ARIT	8.1 (3.0)	7.8	8.5 (2.2)	8.7	0.77
SIM	7.7 (2.6)	7.2	8.4 (3.0)	8.9	2.09
VOC	6.3 (2.7)	5.9	8.3 (2.5)	8.7	6.39 ^a
PCOMP	6.9 (2.2)	7.0	9.2 (3.1)	9.2	3.95 ^{b,c}
PICARR	7.0 (2.9)	7.4	9.3 (3.1)	9.0	1.78
BDES	6.8 (2.3)	6.6	7.8 (2.9)	7.8	1.25
OBJASS	8.1 (3.2)	7.8	9.1 (3.8)	9.3	0.85
CODING	6.2 (3.3)	6.1	8.0 (3.1)	8.0	1.87

^a $p < 0.01$.

^b $p < 0.05$.

^c Duration was significant for PCOMP at 0.05 level.

Jasper, 1954) may also be crucial. In the cited reports of recovery from unilateral cortical damage it is generally assumed that undamaged areas of the same or the contralateral hemisphere assume the functions of the damaged areas. Given the presumed central, subcortical site of dysfunction in patients with tonic-clonic seizures it is not clear that undamaged homologous tissue is available to mediate recovery.

The data from the present study clearly indicate that a child who begins to have tonic-clonic seizures early in life is at risk for future cognitive impairment. The data do not permit a clear determination of the causal factors of this increased risk. Given evidence that commonly prescribed antiepileptic drugs can have a detrimental effect on cognitive development (Cordes, 1973; Stores, 1975) it is possible that the earlier initiation and longer duration of

pharmacological intervention in the early onset group could be a major factor in the observed impairment. The data from the present study do not speak to the important question of whether seizures in young children should be aggressively treated with antiepileptic drugs. The data do, however, point up the importance of further research into the factors underlying the greater impairment seen in children whose seizures began early in life. The wide ranging patterns of deficit seen in the early onset groups make it crucial to determine whether the deficit results from a seizure related variable (e.g., frequency or severity) or whether it is instead a function of the drugs used to suppress the seizures.

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RÉSUMÉ

Quarante huit enfants âgés de 9 à 15 ans souffrant de crises épileptiques tonico-cloniques ont été étudiés avec une batterie de tests neuropsychologiques. Pour huit des quatorze mesures de cette batterie de tests les

enfants dont les crises avaient débuté précocement (avant cinq ans) se sont avérés être significativement détériorés par rapport à ceux dont les crises avaient débuté plus tardivement. Les déficits se sont manifestés pour des tâches nécessitant la répétition d'un acte moteur simple, attention et concentration, mémoire et capacité à résoudre des problèmes complexes. Ces résultats mettent l'accent sur la nécessité de poursuivre les recherches afin de déterminer les facteurs responsables de la plus grande dysfonction observée chez les enfants dont l'épilepsie a débuté tôt dans la vie.

(J. L. Gastaut, *Marseilles*)

RESUMEN

Se ha aplicado una batería de tests neuropsicológicos a 48 niños de 9 a 15 años de edad que padecían ataques tónico-clónicos. Los niños con ataques de comienzo precoz (antes de los 5 años) mostraron incapacidades significativas comparándolos con niños con comienzos más tardíos en 8 de los 14 tests de la batería. Los defectos fueron detectados en las pruebas cuyos requisitos incluían la repetición de un acto motor simple, atención y concentración,

memoria y resolución de problemas complejos. Estos hallazgos indican la necesidad de continuar la investigación para determinar los factores causales de la mayor disfunción observada en el grupo de comienzo precoz.

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ZUSAMMENFASSUNG

48 Kinder (9 bis 15 Jahre alt) mit tonisch-klonischen Krämpfen wurden mit einer neuropsychologischen Testbatterie untersucht. Die Kinder mit einem Frühbeginn der Anfälle (vor dem Alter von 5 Jahren) zeigten sich bei 8 von 14 Tests der Serie deutlich beeinträchtigt im Verhältnis zu Kindern mit späterem Anfallsbeginn. Die Defekte traten bei Aufgaben auf, die folgende Ansprüche stellten: Wiederholung einer einfachen motorischen Handlung, Aufmerksamkeit und Konzentration, Gedächtnis und komplexes Problemlösen. Diese Befunde deuten auf die Notwendigkeit weiterer Untersuchungen, um die ursächlichen Faktoren der größeren Funktionseinbuße zu bestimmen, die bei Patienten mit frühem Anfallsbeginn beobachtet wird.

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