



Antiepileptic drugs, cognitive function, and behavior in children

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ALTHOUGH the majority of children with epilepsy are able to lead relatively normal lives, many are handicapped by learning and behavior problems. A number of factors are related to this, including epilepsy variables such as site of seizure and age at onset of seizure, electroencephalographic (EEG) abnormalities, presence or absence of brain damage, parental attitudes and adverse environmental factors. In addition, antiepileptic medication has in recent years become a focus of attention for researchers. Following a brief review of the literature in this field, some results are reported from a recently completed study at the National Hospitals for Nervous Diseases, Queen Square, London.

ANTIEPILEPTIC DRUGS AND COGNITIVE FUNCTION IN CHILDREN

Many of the earlier studies failed to note clear effects of anticonvulsant medication on cognitive function. For example, Holdsworth and Whitmore¹ in a study of 64 children found no difference in their educational attainment regardless of whether or not phenobarbital was being prescribed. In contrast, Stores,² in studies of children with epilepsy attending normal schools, commented, "phenytoin was associated with poor reading skills, and may have been associated with impaired attentiveness of various types." Bennett-Levy and Stores,³ in a study of 25 children receiving any form of

antiepileptic drug treatment, noted that they had significantly worse concentration, poorer processing ability, and were less alert than 14 children whose antiepileptic treatment had been discontinued. Interestingly, however, children taking carbamazepine alone or sodium valproate alone showed minimal differences from those in a discontinued treatment group.

Some studies have been specifically concerned with trying to dissect out the effect of individual drugs. Most studies of phenobarbital have reported little effect on cognitive function and behavior. For example, in 36 children, Wapner et al⁴ found this anticonvulsant to have no effect on learning after several weeks of treatment. Similarly, Mitchell and Chavez⁵ compared 39 children treated with either phenobarbital or carbamazepine, and carried out psychometric and behavioral evaluations at 6- and 12-month follow-up. They found no significant differences in behavior or cognitive function in the two groups.

Phenytoin has been the subject of remarkably few studies. Although it is known that administration of the drug, even at nontoxic levels, may produce a syndrome of chronic progressive encephalopathy often associated with mental retardation,⁶ the more subtle effects on cognitive function, now well recorded in adults, have been less studied in children.⁷ Stores, as noted, suggested that phenytoin had an effect on reading skills. Nolte et al⁸ investigated two therapeutic regimens in children with epilepsy. The children were assigned to a high- or low-plasma level group, and were assessed before and 6 months after starting treatment with phenytoin. A group of six healthy children in the same age range served as controls. All children were tested twice on a variety of cognitive tasks, their IQs

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being within the average range. Improvement on some tests was found on the second trial for all groups, as might be expected because of a practice effect. However, the high-plasma phenytoin group (mean, 22.0 mg/L) showed a reduction in mean scores. The children were seizure-free over the 6-month period, but these data suggest that phenytoin at higher levels may affect performance.

In an investigation of the relationship of serum and red cell folate levels and phenytoin to cognitive and behavior disturbances in a population of children with intractable epilepsy, Trimble and Corbett⁹ reported that folate levels were significantly lower in children with intellectual deterioration, and that the children with the lowest folate levels were significantly more likely to be receiving phenytoin. In that study, children showing signs of cognitive deterioration, with a fall in IQ of greater than 10 points over a 12-month period, had significantly higher serum phenytoin levels than children without such signs.

Early reports of sodium valproate suggested improvements in alertness following its administration, but systemic confirmation of this has yet to be demonstrated. In contrast, there are occasional reports of an encephalopathy with stupor, which may be seen with monotherapy. Aman et al¹⁰ used an extensive battery of psychological tests to study 46 children with well-controlled seizures, who were on monotherapy with the drug. They compared differences in performance before or after the morning dose, taking advantage of fluctuations in the pharmacokinetic profile of the drug. Generally, patients on lower doses performed best, but time of dose seemed to have no effect on performance.

Carbamazepine has been the subject of several studies, and rather like sodium valproate, favorable reports of its effects on cognitive function have been noted since its introduction. Martin et al¹¹ studied 15 epileptic children prior to the addition of carbamazepine to their existing drug regimen, and then followed them, giving them a variety of cognitive tasks. There was an average rate of improvement of 34%, with 52% of the children's scores remaining unchanged. Marked improvements were reported on progressive matrices, and on tests of speed and visuomotor coordination. In contrast, some showed a decline in skills necessary to complete the Goodenough Draw-a-Man test. Schain et al¹² withdrew barbiturates from children and substituted carbamazepine, testing the children 4 to 6 months later on a variety of cognitive tests. A statistically significant improvement occurred on all measures taken, and parents and teachers reported improved

attentiveness and alertness.

Rett¹³ studied three groups of children: the first group were being changed to carbamazepine monotherapy, the second were receiving carbamazepine monotherapy, and the third were taking other anticonvulsants. Psychological testing was carried out on two occasions separated by an interval of 11 to 12 months. In those children receiving carbamazepine alone, a significant improvement in a test of psychomotor function was noted.

Jacobides¹⁴ studied 46 children before and after treatment with carbamazepine over one school year. Improvements on school marks for arithmetic rose by an average of 22%. This was most marked for those children whose intellectual ability was average or above. IQ scores generally increased from a mean of 87 to a mean of 100, and improved alertness was reported in most patients. In this study, statistical comparisons were not given, and a control group was not available. More recently, Mitchell and Chavez¹⁵ studied 30 children treated with either phenobarbital or carbamazepine for newly diagnosed partial onset seizures. No differences were noted in the effects of these drugs on cognitive function, but the only scales used were the WISC-R and the McCarthy scale of children's abilities. In contrast, Holcombe et al¹⁶ studied children between the ages of 5 months and 5 years who were started on therapy with either carbamazepine or phenytoin. While no significant changes were noted in developmental quotients, motor control, or memory, patients receiving carbamazepine showed improvement in overall attention span, a parameter shown to be adversely affected by pretreatment with phenobarbital.

Assessment of other anticonvulsant drugs has been problematic. For example, ethosuximide is generally used in children with spike-wave activity of 3 per second, the improvement in the EEG being associated with improvement in cognitive abilities. The effects of this drug on cognitive function are mixed, some authors reporting improvement, others reporting deteriorations.¹⁷

Separating the effects of primidone from those of phenobarbital has been difficult, although Trimble and Corbett⁹ noted higher concentrations of primidone in children at a special school who had a deterioration of their IQ.

Clonazepam, while not the subject of a systematic study, is thought to be a sedative compound, and certainly in volunteer studies in adults has been shown to provoke cognitive impairment, in contrast to clobazam, a 1,5-benzodiazepine, which is much less likely to

impair cognitive performance.¹⁸

ANTICONVULSANT DRUGS AND BEHAVIOR

Studies of the effects of anticonvulsant drugs on behavior are even fewer than those that relate to cognitive function. Mellor and Lowit¹⁹ noted that children receiving phenobarbital alone had the same incidence of behavior disorders as those not on the drug, but they also observed that children treated with other anticonvulsants, with or without phenobarbital, showed a higher incidence of behavior problems. Hoare²⁰ reported that children on phenytoin in addition to another drug were more likely to be behaviorally disturbed than children on phenytoin alone, those data suggesting that polytherapy may be a complicating factor in behavior problems.

There is more general agreement that phenobarbital influences behavior, although few studies of this have been made. In the investigation of Trimble and Corbett,⁹ the parents' and teachers' behavior rating scales devised by Rutter were used to assess behavior problems in a population of children with difficult-to-control epilepsy. It was reported that half the children on phenobarbital had some form of conduct disturbance. Ingram²¹ specifically studied the relationship between phenobarbital and behavior. Fourteen hyperactive children aged 4 to 12 years, eleven of whom also had epilepsy, and who all showed evidence of cerebral damage, were given phenobarbital for an unspecified period. No change in behavior occurred in four, and two were reported to show diminished activity; but in eight there was a definite exacerbation of hyperactivity and a tendency to aggressive outbursts. In the children with epilepsy, seizure frequency was reduced or abolished in eight.

With regard to phenytoin, Ingram²¹ noted that of seven children with epilepsy and overactive behavior who were prescribed this drug, attacks were reduced or abolished in four, and were unaffected by the drug in three. No clear associations between phenytoin and behavior emerged from this study or from the study of Trimble and Corbett.⁹

One study has assessed the behavioral effects of sodium valproate, using serum level monitoring. In 64% of children given the drug, Herranz et al²² noted behavior changes, which included irritability, hyperactivity, lassitude, drowsiness, absentmindedness, sadness and aggression. Plasma levels were significantly higher in patients who presented with lassitude and

drowsiness, but this report did not provide information on assessment of patients prior to introduction of the drug. Nevertheless, there is a suggestion that a relationship may exist between serum levels of sodium valproate and subsequent behavior changes.

Carbamazepine has generally been reported to have a favorable influence on behavior, although adverse idiosyncratic behavior problems including psychosis have been noted.²³ Further, many of the systematic studies have been carried out on children with behavior disturbances, with or without EEG abnormalities, but often with no evidence of a seizure disorder. For example, de Weis et al²⁴ investigated 33 children with disorders of conduct and EEG abnormalities. A double-blind comparison between carbamazepine (mean daily dose 300 mg/day) and placebo was carried out. Behavior was evaluated by psychiatric and psychological interviews with the children and their parents. A statistically significant improvement in symptoms was found for the drug group in 15 of 17, compared with 8 of 16 of the placebo group. Similarly, Groh et al²⁵ carried out a double-blind crossover trial against placebo on 20 children of normal intelligence with a variety of behavior problems. The 6-week treatment periods were separated by a therapy-free interval of at least 4 weeks. Behavior was evaluated with a 39-item questionnaire completed by parents and teachers. There was a highly significant difference with respect to change noted on placebo or drug, the greater improvements being noted with the drug. A definite improvement was seen in ten children, six showed a moderate improvement, and there was no change in three. One subject in the active compound group showed a deterioration.

STUDIES OF FEBRILE CONVULSIONS

Several studies have attempted to assess development and behavior in children given anticonvulsant drugs prophylactically following one or more febrile convulsions. However, these are of necessity limited to phenobarbital and sodium valproate. Ellenberg and Nelson²⁶ noted that the mean IQ for 18 children who received prophylactic phenobarbital was similar to that for a control group. Aldridge-Smith and Wallace²⁷ tested 16 children before they were given phenobarbital and at intervals throughout the subsequent two years of follow-up. Although these children had no further convulsions, they did show small rises in their developmental quotients that were slightly but not

significantly less than those achieved by 21 children who were given no anticonvulsant therapy. Camfield et al,²⁸ in a double-blind placebo-controlled study of phenobarbital given to prevent recurrent febrile convulsions, assessed children either on the Bayley Scale of Infant Development, which yields a score equivalent to the IQ, or the Stanford Binet Scale. Thirty-five children received the drug, and 30 received placebo. They were tested between 8 and 12 months after treatment was initiated. No significant differences between the groups were noted. However, when the serum phenobarbital concentration at the time of testing was correlated with five Binet subtest scores, a significant negative correlation to memory scores was noted. In addition, children receiving the drug for 12 months had significantly lower general comprehension scores than those tested after only 8 months.

With regard to behavior, Heckmatt et al²⁹ noted that 16 of 88 patients receiving phenobarbital developed behavior problems which improved in 12 on stopping treatment. The study of Camfield et al²⁸ asked parents about side effects, especially sleep disturbance, behavior change and hyperactivity. In the phenobarbital group, dose-related adverse effects, especially sleep disturbance and "daytime fussiness" were predominant. The investigators reported that children would wake for several hours in the early morning, and this was often associated with daytime fussiness and irritability. Interestingly, no hyperactivity was observed in this study.

Bacon et al,³⁰ in another comprehensive study, gave phenobarbital, phenytoin or placebo for 12 months to 138 children who had had their first febrile convulsion before their second birthday. The changes in the children's behavior were assessed, using a standardized questionnaire completed by the mother. This form was filled out on three occasions: before treatment, and 3 weeks and 9 weeks following treatment. No significant differences were noted between a phenobarbital and a control group. At the end of a year's treatment, however, the questionnaire was answered again by the mothers of 62 children, and four significant differences emerged for the children taking phenobarbital. Twenty-three percent were reported as becoming hyperactive, 15% as less fidgety, 19% as more shy, and 36% as having disturbance of appetite. Much lower percentages of disturbance were recorded for the phenytoin and placebo groups. In this study, the amount of behavior change was thus rather small. An important feature of the study was that salivary concentrations were kept below 13.7 mg/L.

Wallace and Aldridge-Smith³¹ gave phenobarbital or sodium valproate or no treatment to 121 consecutive patients admitted for first convulsions. Parents were asked to rate their children's preconvulsive behavior, with reassessment at 12 and 24 months later. There was no significant difference in seizure frequency between the two drugs, but twice as many children on phenobarbital had deterioration in at least one aspect of behavior in comparison to the sodium valproate group, whereas the parents of five reported improved behavior.

POLYTHERAPY AND THE REDUCTION OF ANTICONVULSANT PRESCRIPTION

There is at least a hint in the above literature that polytherapy itself may bring adverse consequences for behavior and cognitive function in children, as it does in adults.³² We have completed a series of studies in which alteration of anticonvulsant prescriptions in children has been evaluated, the cognitive status of the children being rated by a series of microcomputerized tests, and questionnaires being completed to assess behavior.

An automated test battery essentially examined perceptuomotor performance, attention and sensory processing, central cognitive processing and memory. Behavior was assessed with the Connors Parent Symptom Questionnaire (CPSQ)³³ and the Children's Depression Inventory (CDI).³⁴ This latter is a modification of the adult Beck Depression Inventory, which allows children to assess their own mood.

Forty-four children with epilepsy, aged 7 to 17 years, and 21 nonepileptic children aged 7 to 12 years were assessed on three occasions over a period of 6 months, separated by three monthly intervals.³² The control group was compared with three subgroups of children as follows: the first remained on the same anticonvulsant regimen throughout ($n = 18$); the second underwent a decrease in dosage or number of drugs ($n = 16$); while the third had an increase in dosage or number of drugs ($n = 10$). The three epilepsy groups were comparable with respect to age and full-scale IQ, which was within the average range. The normal control group had a significantly lower age and higher full-scale IQ, but these differences were co-varied for in the statistical analysis. There was no significant change in seizure frequency for the three epilepsy groups over time.

In these investigations, clear differences were noted between the increase and decrease groups on a number

TABLE 1
SIGNIFICANT DIFFERENCES (IN RESPONSE LATENCY)
BETWEEN CHILDREN RECEIVING POLYTHERAPY AND THOSE
ON MONOTHERAPY WITH EITHER CARBAMAZEPINE OR
SODIUM VALPROATE

Reaction time (3 tasks)
Coding
Digit matching
Immediate recognition memory for faces
Perceptual identification
Semantic memory (i.e., accessing previously stored information)

of cognitive tasks and on the behavioral questionnaire. Thus, increasing the antiepileptic drug load had a detrimental effect on the time taken to complete a task of simple perceptual identification of stimuli and the time taken to access previously stored information. The decrease group, in contrast, showed improved performance on a face recognition task not exhibited by the other groups. On the behavior questionnaire, the greatest improvement in score over time on the CPSQ was seen in the decrease group, with regard to the total score and to some subfactors such as conduct, anxiety and learning problems. In particular, the children decreasing their anticonvulsant drug load showed a significant decrease in scores on the CDI, no changes in behavior on this or the CPSQ being noted in the group whose drug load was increased.

DIFFERENCES BETWEEN INDIVIDUAL ANTICONVULSANT DRUGS IN CHILDREN

In this investigation, it was also possible to compare and contrast the performance over a 6-month interval of three groups of children taking different drug regimens. A group on polytherapy ($n = 14$) and a group on constant carbamazepine or sodium valproate monotherapy ($n = 21$) showed no difference in age at onset, and after co-varying for seizure frequency, several significant differences, as shown in *Table 1*, were noted.

Further, when children receiving carbamazepine monotherapy ($n = 12$) were compared with a group on sodium valproate monotherapy ($n = 9$), again taking seizure frequency into account, some significant differences favoring carbamazepine were noted with respect to response latency. These tasks (*Table 2*) included changes on reaction-time tasks, a coding task, a digit matching task, and a semantic memory task measuring time taken to access previously stored information.

When behavior measurements were analyzed, no

TABLE 2
RESPONSE LATENCY DIFFERENCE BETWEEN CHILDREN ON
CARBAMAZEPINE AND SODIUM VALPROATE MONOTHERAPY
IN COGNITIVE FUNCTION STUDIES

Reaction time (2 tasks)
Coding task
Digit matching
Semantic memory (i.e., accessing previously stored information)

significant differences were noted between the groups. Interestingly, on the CDI, the only group to show changes over time was the carbamazepine group, which showed a significant decrease in scores over the 6-month time interval of the investigation.

SUMMARY AND CONCLUSIONS

In conclusion, it should be repeated that behavioral and cognitive functions in children with epilepsy, as in adults, represent the outcome of multifactorial processes. However, interest has been growing in the role of anticonvulsant drugs as an important variable. Studies in adults have clearly shown the impact of these drugs on both cognitive function and behavior,³² and the beneficial effects of achieving monotherapy, especially with carbamazepine, have been noted. Extrapolation of these results to children would seem reasonable, and there is some evidence in the literature to support this conclusion. Data in children, however, are complicated by several confounding factors. These include the status of the child under investigation; for example, children with a pre-existing behavior disorder appear to be more susceptible to developing grossly disturbed behavior with medications such as phenobarbital, as opposed to those who at pretreatment assessment do not display abnormalities. Mentally retarded children may be another group specifically susceptible to developing problems with medications. The effect of the anticonvulsant drug on seizure frequency is a complicating variable in interpretation of many investigations: in some patients improvement of seizures leads to improved behavior, while in others the opposite occurs. In some children, behavior exacerbations appear to be provoked by the sudden cessation of seizures, which may occur, for example, in forced normalization associated with barbiturates or benzodiazepines.³⁵ Serum level monitoring is often not possible in childhood studies because of ethical considerations, and interpreting pharmacokinetic interac-

tions from mere knowledge of orally prescribed agents is hazardous.

In considering the influence of anticonvulsant drugs on behavior and cognitive function, it would seem that phenobarbital is more likely to impair behavior than cognitive function, while sodium valproate and carbamazepine have the least effects on both these variables. The influence of phenytoin has yet to be clarified. In our own study we have been able to identify differences between the effects of sodium valproate and carbamazepine on cognitive function, with results favoring carbamazepine; but we did not find differences in behavior. As with adults, polytherapy is probably detrimental both to behavior and to cognitive function, and in our investigation, rationalization of polytherapy has led to significant and measurable improvements. It is important to consider such data when one selects anticon-

vulsants for children, since in many cases they will be taking these drugs for the rest of their lives.

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