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Cognitive Deficits in Epilepsy

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Abstract

Cognitive disturbances have been observed in adults and children with epilepsy. Research in the past three decades has unravelled the gross and subtle nature of these cognitive deficits. Intelligence, memory, attention, motor speed, mental speed and perceptuo-motor functions are impaired. Learning disabilities are present. Intelligence tests, neuropsychological batteries and comoputerized tests have been used to assess cognitive functions. Factors which affect cognitive functions are etiology, type of seizure, seizure frequency and duration, age of onset, EEG abnormalities, and the nature of treatment. Anticonvulsant drugs impair cognition. Polypharmacy is associated with greater deficits. Barbiturates and phenytoin even when given as monotherapy result in significant impairment. The clinical variables exert a combined effect. Cognitive dysfunction affects the learning of the child and the work performance of the adult and also results in behavioral problems. The ill effects of impaired cognition has led to the formulation of treatment goal as reduction of seizures, with adequate cognition.

Key words -
Epilepsy,
Cognition,
Neuropsychology,
Neuropsychological tests,
Anticonvulsants

The association of epilepsy with cognitive dysfunction is long standing. More than 100 years ago Gowers made the first observation on the subject [1]. Over the years the nature of this association has been examined from various perspectives. Advances in the understanding of cognition; refinements in assessment procedures; comparisons of the relative efficacy of antiepileptic drugs (AEDs), a better classification of epileptic patients each contributed to a delineation of the patterns of cognitive impairment. The problem assumes importance in the light of

(a) the effect of impaired cognition on behavior;
(b) the inescapability of treating an epileptic patient with antiepileptic medication though the medication can lead to cognitive deficits;
(c) availability of choice among the AEDs.

Earlier studies viewed cognitive dysfunction as an unitary entity. Until about thirty years ago, cognitive dysfunction in epilepsy was characterized as intellectual decline, which was evident on intelligence tests. The tests such as Wechsler Adult Intelligence Scale (WAIS) measured intelligence as an entity. Advent of neuropsychological assessment as a means

of assessing brain dysfunction changed the emphasis from an unitary view of intellectual decline to one where particular abilities were impaired. The sixties and seventies saw the emergence of assessing the pattern of brain dysfunction using neuropsychological batteries such as the Halstead Reitan and the Luria Nebrasks batteries. These researches culminated in the development of neuropsychological battery for epilepsy which contained tests sensitive to cognitive dysfunction in epileptic patients [2]. In the last decade computerized tests to measure subtle deficits in the areas of attention and information processing has emerged [3], [4]. Electrophysiological indices of cognitive dysfunction is also being identified [5], [6], [7].

Previously studies were largely conducted on chronic institutionalized epileptics. The trend has changed and in the last decade cognitive dysfunction of newly diagnosed epileptics with well controlled seizures has been studied [8]. Clinical variables which affect cognitive functioning are being controlled [9], [10]. With these, refinements of sample selection and assessment procedures, the diverse manner of presentation of cognitive dysfunction is recognized. Curtailment of cognitive dysfunction is now a necessary condition to fulfill in the treatment of epilepsy [11], [12].

Nature of Cognitive Deficits

Intelligence:

Reduced IQ is associated with epilepsy, wherein the loss of ability is correlated with the number of seizures [13]. A fall in IQ i.e., the verbal, performance and full-scale IQ occurs in epilepsy associated with increasing number of seizures and the occurrence of status epilepticus [14]. In a large group of epileptics, IQ as measured by WAIS was normal prior to the commencement of AEDs [15]. Epileptic children have lowered IQ compared with normals [16]. Even when epileptic children have a normal IQ, performance IQ was lower in partial epilepsy [17]. In children, fall in IQ was found with toxic levels of AED, presence of more than one seizure type, symptomatic epilepsy and early age of onset [18]. Fall in IQ over a 5 year period was present even when the seizures were well controlled, patients were on fewer anticonvulsants and EEG had improved [19].

Neuropsychological deficits:

Neuropsychological assessment using standardized neuropsychological batteries has been undertaken on epileptic patients. Halstead - Reitan neuropsychological battery was used to compare epileptic patients with and without brain damage with normal controls and brain damaged patients without epilepsy. Epileptics with brain damage had greater deficits as compared with epileptic patients without brain damage. The performance of epileptic patients was inferior to that of controls [20]. In a multicentre study epileptics had impaired neuropsychological abilities on i.e., general intellect, attention and concentration motor speed and motor manipulation even before AEDs were commenced [15]. Neuropsychological deficits exist in epileptic children [16], [21]. Speed of information processing, memory, vigilance, alertness, sustained and focussed attention, motor fluency are the cognitive domains particularly vulnerable to epileptic factors [4]. Frontal lobe functions of attention, kinetic melody, susceptibility of short term memory under interference were observed in epileptic children [22]. Recently computerized tests are used to assess cognitive deficits. "Fepsy" computerized battery used in children measures memory, attention, problem solving, visuomotor performance, language and cerebral dominance [23]. The other battery used on adults and children measures immediate and delayed memory, attention, speed of registration of new information, perceptual and motor speed [3]. Assessment on computerized battery is linked to online EEG to monitor the effect of subclinical seizures on cognitive functioning [23].

Memory deficits:

Deficits in learning and memory functions have been recorded for more than 100 years [24]. Memory deficits are subjectively reported often in the epileptic clinic [8]. Epileptic patients performed poorer on the Boston memory scale as compared to normals [25]. Initial registration, of numbers and geometric figures was poorer, compared with learning in patients whose epilepsy was well controlled, indicating that short term memory was more impaired than learning [8]. Immediate and delayed memory for verbal and visual material was impaired, which was mainly due to poor recall, in patients with well controlled epilepsy [26]. Longterm storage and retrieval from long term memory was impaired for verbal and visual material. Deficits of short term storage was also present. Encoding of information could be slowed down, as patients require a greater number of presentations to learn [27]. Frequent and longer presentations of the material improve the memory scores [28]. Automatic encoding of frequency and spatial information is poor and learning is effortful in epilepsy [29].

Studies on patients who have undergone unilateral lobectomy for intractable epilepsy indicates that verbal memory deficits are associated with left-sided lesions, and visual memory deficits with right-sided lesions [30]. In patients with temporal lobe epilepsy who have not undergone surgery, the findings are not unclear. Verbal memory deficits associated with left-sided lesions have been found in children [31] and adults [32]. However patients with right sided lesions did not have deficits of nonverbal memory [24]. Left temporal lobe epilepsy was associated with poorer verbal learning ability, impaired immediate memory, poor retrieval of verbal learning and recall, but patients with right-temporal epilepsy performed as well as controls [33]. Laterality of memory deficits were absent, when tested with the Wechsler memory scale [34].

Attention deficits:

Attention is impaired in epileptic patients [26], [31], [35]. The tests of attention used have been the continuous performance test to measure sustained attention [31], detection of briefly presented visual targets [35]. Letter-figure substitution to measure speed; the zazzotest wherein one or two types of tailed squares are crossed out among other tailed squares to measure choice; the stroop test to measure decision-making and flexibility have been used [26]. Inattentiveness has been observed in the setting. Epileptic children were rated as being inattentive by teachers [36], [37]. Memory deficits have been attributed to attention deficits, as these two deficits coexist and attention is a pre-requisite for the adequate registration of the to-be-remembered material. Co-existence of attention and memory deficits has been observed in epilepsy [31], [34]. Stroop test has found deficits of attention and concentration in epilepsy [3]. A general slowing revealed by increased search times on a visual search task and reduced alertness are found in epileptic children [23].

Speed of mental processing:

Simple and complex reaction time are slower in epileptic patients [38]. Reaction time slowing using computerized tests have been observed in epilepsy [3], [27]. Performance on the Bender Gestalt tests is impaired in children [39] and adults [40] with epilepsy.

Learning disabilities:

Epileptic children, even while studying at an age appropriate class were frequently impaired in arithmetical ability [41]. In another study fewer epileptic children (17%) were rated high in mathematical ability compared to controls (31%) [42]. Reading attainment is delayed i.e., epileptic children were reading at a level below their chronological age [43]. Spelling errors and poor writing is

also present. Three subtypes of learning disability have been identified, i.e.
(a) 'memory-deficit type' with specific deficits of short term memory associated with temporal lobe dysfunction;
(b) 'attention-deficit' type wherein several academic skills are affected and a high frequency of tonic-clonic seizures are present;
(c) 'speed-factor' type exhibiting slowing of information processing especially in complex task configur [44].

Causes of Cognitive Deficits

The two causes of cognitive deficits in epileptics are the underlying brain pathology and the nature of treatment [12]. Epilepsy can be symptomatic or idiopathic. An idiopathic epilepsy is often characterized by the presence of a family history, normal neurological development, absence of signs of neurological disease other than epilepsy, a spontaneous remission of seizures later in life, a good response to the appropriate antiepileptic drug but a continued tendency to seizures. Idiopathic syndromes are pyknoleptic petitmal, juvenile myoclonic epilepsy, primary generalized epilepsies and benign partial seizures of childhood. Cognitive deficits are not common in idiopathic or primary epilepsies. Symptomatic epilepsy is characterized by impairment of neurological function or development apart from that contributing to seizures. The widespread dysfunction can result in cognitive deficits such as impaired cognitive development or functions. Specific cognitive deficits is linked to the specific location and amount of brain dysfunction. Inflammatory, neoplastic and metabolic disorders and CNS infections can result in symptomatic epilepsies. Epileptic patients with known brain pathology have a greater neuropsychological dysfunction than patients in whom the aetiology is unknown [20]. Children with symptomatic epilepsy have lower IQ scores, poorer scholastic performance, while those with idiopathic epilepsy are more likely to have IQs in the normal range [45].

Epileptic seizures if uncontrolled may lead to consecutive neuronal changes in areas of brain directly involved in the elaboration of the epileptic process and in areas far removed, which can affect learning, abstraction, information processing and memory [12]. Functional brain imaging techniques, such as PET and SPECT have demonstrated that epileptogenic foci may be regarded as "functional lesions" associated with functional and structural pathological changes in specific parts of the brain. Epileptogenic foci in the left hemisphere are associated with impairment of verbal learning, verbal memory and serial information processing. Naming problems are more prevalent with left posterior EEG abnormalities. Right-hemisphere foci are associated with deficits of visuo-spatial tasks, directed attention, modulation of affect, paralinguistic aspects of communication and parallel information processing. Temporal lobe dysfunction is associated with memory and learning problems, while frontal lesions show impairment of attention and memory and learning problems, while frontal lesions show impairment of attention and memory [23].

Treatment with anticonvulsant drugs and surgery can be accompanied with cognitive deficits. Introduction of AED medication in untreated epileptics aggravates the already present cognitive impairment [15]. Polytherapy is harmful to cognitive functions [18], [23], [46], [47]. Reduction of the number of AEDs is associated with improved cognitive functioning in the areas of concentration and motorspeed [3]. Examination of the cognitive side-effects of individual AEDs has been undertaken

since the late 70s [48]. Sedative drugs such as phenobarbital, primidone and benzodiazepines impair cognitive functions to a comparable degree. Phenytoin and carbamazepine also impair cognitive functions though their tolerance is greater than the sedative drugs [50]. Phenytoin is associated with a greater degree of impairment [3], [46], [53] carbamazepine with least [48]. Attention, problem solving, performance on visuomotor tasks, and motor speed are adversely affected with phenytoin [52], [54]. Phenytoin is associated with deficits in concentration, memory, mental and motor speed, when the serum level is high but within the therapeutic range [55]. Carbamazepine facilitates problem solving [54]. It has some adverse effects on task performance which is less compared to phenytoin or phenobarbital [52]. Even in newly diagnosed patients on monotherapy the effects are visible in that, attention, memory and concentration is better compared with phenytoin [56]. Addition of carbamazepine results in improved concentration and memory [3]. Carbamazepine treated patients showed only minimal changes on measures of attention, memory, mental speed between high and low serum levels. Motor speed was unimpaired [55]. Immediate memory and motor speed were better in patients on carbamazepine, compared with phenytoin primidone or phenobarbital [57]. Valproate produces minimal effects on psychological tests [52], but still does affect memory and perceptuo-motor abilities [40]. High serum levels are associated with deficits on attention, memory, mental and motor speed [55]. A recent comprehensive multicentered study has however indicated that the four major AEDs i.e. phenobarbital, phenytoin, primidone and carbamazepine impair cognitive functions to a similar degree. The cognitive effects of AEDs are not substantially different, when the seizures are controlled and chronicity is absent [57]. Withdrawal of sodium valproate, carbamazepine and phenytoin did not have differential effects on cognitive functions excepting that mental speed was adversely affected by phenytoin [58]. Cognitive deficits can result due to surgical procedures employed in the treatment of intractable epilepsy. The neuropsychological outcome of anterior temporal lobectomy is usually good. Overall intelligence, achievement and language functions are usually unimpaired. However left-sided lobectomies may be associated with word-finding difficulties and verbal memory; while right-sided lobectomies may have visuo-spatial and memory difficulties [12]. Corpus callosum sectioning can be accompanied by memory deficits [59].

Clinical variables associated with epilepsy are also known to affect cognition. Apart from the etiology and nature of treatment discussed above, age of onset, type of seizure, seizure frequency, duration of disorder and the presence of EEG abnormalities are some of the other clinical factors which influence cognitive functioning.

Age of onset:

Early age of onset of epilepsy is associated with greater neuropsychological deficits. Patients with epilepsy commencing before the age of 5 years had lowered IQ and impaired neuropsychological functions compared to patients with a later age of seizure frequency [60]. Memory, attention, motor speed, and problem solving were impaired in patients with an early age of onset, after controlling for duration effects [61]. IQ progressively decreased, though within normal limits with earlier ages of onset [62]. Learning disabilities were greater when the age of onset was early [41].

Seizure type:

Myoclonic, tonic, atonic, clonic and tonic-clonic seizures are associated with the poorest mental abilities, while generalized nonconvulsive seizures ("petitmal") and partial seizures are not associated with substantial cognitive deficits [62]. Patients with generalized seizures performed less well on the Halstead Neuropsychological Test Battery and the Wechsler Adult Intelligence Scale compared to

patients with partial seizures [20]. Patients with secondarily generalized seizures had lower intellectual performance than those with partial seizures or primarily generalized seizures [15]. Children with generalized epilepsy had greater neuropsychological deficits [16]. Memory deficits have been associated to a greater extent with complex partial seizures [34]. Children with temporal lobe epilepsy had impaired memory, while those with centraencephalic epilepsy had normal memory [31]. Sustained attention was impaired to a greater extent in generalized epilepsy as compared with focal epilepsy in adults [35] and in children [31]. Learning disabilities, especially deficits on arithmetic were greater in absence and tonic-clonic seizures as compared with other seizure types [41].

Seizure frequency:

Seizures are implicated in neuronal damage [63] and frequent seizures can be expected to result in greater cognitive dysfunction. Findings are not uniform. Frequent seizures are associated with marked cognitive impairment [9], [22], [60] but other studies did not find it to be so [64]. Lack of consistency could arise because seizure frequency is computed over a relatively short period such as the previous few years or months [62]. Calculation of lifetime seizure frequency has indicated that when the number of generalised tonic-clonic seizures exceed 100 significant cognitive impairment i.e. on both IQ and neuropsychological functions are present. A single episode of status epilepticus lasting for 30 minutes or more resulted in impaired cognition even if the total number of seizures were fewer [14]. In epileptic children learning disabilities, especially deficiency of arithmetical skills were greater when the lifetime seizure frequency was higher [41].

Duration of disorder:

Longer duration of disorder is associated with diminished mental abilities, but the association is weak as the degree of seizure control varies. A new index, "years with seizure" accounts for both variables; wherein only those years in which seizures occurred are counted. It is strongly associated with cognitive impairment [62]. In well managed epileptic children neuropsychological impairment was not associated with longer seizure duration [22].

EEG abnormalities:

Depth recording has indicated that subclinical epileptic discharges may interfere with cognition [65]. Studies with surface recordings found an association between impaired neuropsychological functioning and frequent epileptiform activity on the EEG [66]. Nonepileptiform abnormalities such as slowing of background rhythm, presence of large amounts of theta activity, and a combination of slow waves and epileptiform activity were associated with cognitive deficits, particularly the combination factor [67]. In absence seizures the 3/s spike-wave activity is associated with impaired reaction time and vigilance [68]. Generalized subclinical spike-wave discharges are associated with transitory cognitive impairment, especially on intellectually demanding tasks [5]. The adverse effects of the above clinical variables on cognitive functions is not unitary but interactive, hence is better studied in a multifactorial design [9], [10].

Treatment of Cognitive Dysfunction

Impairment of cognition has different effects in the adult and child patients. In children, it can significantly impair the learning process, thereby hampering the child's future capabilities. Adjustment

at school can be affected due to behaviour problems consequent to cognitive dysfunction. The inattentive epileptic child may be punished leading to maladaptive behaviour at school which can generalize to other settings. In the adult, cognitive deficits can affect the work performance which can lead to maladjustment in several spheres. Transient attentional deficits accompanying subclinical seizure discharges can be hazardous. The treatment of cognitive dysfunction is still in its infancy. Cognitive impairment has been recognized in its gross and subtle forms and the importance of reducing it has been emphasized. In adults, reduction of polytherapy; a judicious choice of the AED keeping its side-effect on cognition in view; prevention of drug toxicity by careful monitoring of drug serum levels are some of the clinical procedures adopted to reduce cognitive dysfunction. Patients reporting memory deficits have been taught with success association and chaining methods to improve memory [69]. In children teachers and parents are counselled regarding the child's cognitive abilities to reduce overprotection, overexpectation, or rejection and undue criticism consequent to its cognitive dysfunction. Neuropsychological rehabilitative strategies aimed at improving specific deficits are yet to be tried. In view of the detailed understanding of cognitive impairment, the development of remediation programmes based on appropriate cognitive retraining techniques is required.

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