DIFFICULT TO CONTROL EPILEPSY IN CHILDHOOD – A LONG TERM STUDY OF 123 CASES

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ABSTRACT

One hundred and twenty three children with difficult to control epilepsy (DCE) were studied. Etiological factors which predominated included an age of onset less than 2 years (71.5%), male sex (69%), mixed, secondarily generalized, or complex partial seizures (77%), mental retardation (64%) and neurological abnormalities (52%). Static neurological disease was seen in 63%, with only 17% having idiopathic disease. Identifiable epileptic syndromes were noted in less than half the children. The surface EEG was abnormal in 84%, and correlated with the clinical seizure type in 81%. CT and MRI were helpful in diagnosis in only 38 and 48%, respectively, and even less so in therapy decisions, 7 and 16%, respectively. Prior therapy revealed the use of polytherapy in 61% and sub-optimal dosages in 78%. In the 100 patients with adequate follow up, 67% showed a good response, i.e., 35% complete and 32% more than 50% reduction in seizures. Only 11% were total non-responders, and most wee severely retarded. Major treatment strategies employed included switching to monotherapy, supranormal dosages and avoidance of sedative anticonvulsants. Side effects were noted in 41% with 8 cases being life threatening. Overall mortality was 4%. We concluded that risk factors for DCE included early age of onset, mental retardation and certain seizure types. EEG was more helpful than neuroimaging. Treatment responses were favorable, especially in those with normal intellect and the use of normal or high dose monotherapy.

Key words: *Refractory Epilespy.*

Difficult to control epilepses (DCE) form a small but significant component of all epilepsies in childhood. These epilepsies, being resistant to treatment, are a source of considerable frustration to the child, parents as well as the attending physicians. An adequate knowledge of which epilepsies are likely to be difficult to control, and of the treatment strategies that are likely to produce the best response, goes a long way in the optimal management of these patients. Our department evaluates a disproportionately large number of such cases. We decided to study these cases in terms of etiology, predisposing factors, prior treatment and how they responded to various treatment strategies. Our aim was to build a clinical profile of the difficult to control epileptics, assess the various risk factors and the various treatment strategies.

Material and Methods

Records of epileptic patients were reviewed and patients with DCE identified. Patients were labelled as DCE on the basis of seizures: (*a*) which were frequent and/or severe enough to disrupt normal childhood activities, and (*b*) which had remained refractory for a period of atleast 6 months before evaluation by us or were resistant to conventional therapy over a 6 months follow-up with us. Only those who had followed up with us for atleast 4 months were considered for follow-up analysis.

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A total of 123 patients were included in the study. These cases wren analyzed for the following: age of onset, sex, duration, frequency, type of seizures, family history, presence of neurological abnormalities, mental retardation (MR), type of epilepsy, epileptic syndrome if any, EEG and imaging results, and the response to prior treatment.

Frequency, duration, age of onset and seizure type were decided not only on the basis of record review, but also on subsequent detailed history taking from the relevant witness on follow up, usually on multiple occasions, with re-enactment of the phenomenon. Multiple examinations were performed to determine central nervous system (CNS) abnormalities and MR. On occasion, video recordings made by the parents were reviewed.

Patients coming regularly for follow-up were then further assessed. Those coming infrequently were contacted telephonically or by postcard and follow-up was obtained. One hundred cases had a follow-up for at least 4 months or more with us, extending upto 42 months (mean 18.45 months), which was adequate enough to assess the response to 2 or more treatment strategies. Twenty three cases considered difficult to control before evaluation by us did not come for a regular follow-up and hence only the various risk factors were analyzed in these cases. The 100 patients with adequate follow-up were further evaluated for the response to treatment, correlation of the response with CNS examination, presence of MR, underlying disease and epileptic type. Adverse effects of therapy and ultimate outcome at the end of the study were also assessed.

The following terminology was used in evaluation: Seizures were classified clinically according to the ILAE, 1981(1) definition as being partial/localization related *vs* generalized. *Static CNS disease/encephalopathy* and *progressive CNS disease/encephalopathy* were defined on well known criteria(2). Patients with normal CNS, mentation and imaging were called as *idiopathic*. CNS findings were subcategorized as either *normal, equivocal or abnormal.* MR was determined as per IQ estimation or clinician's assessment of development as per the Denver Developmental Scale. To assess a response each strategy was used for at least 2 months (usually several months) prior to making any change. Various strategies used included: (*i*) *Normal dose monotherapy*– use of a single drug in pharmacologically accepted doses; (*ii*) *High dose monotherapy*– Use of carbamazepine (CBZ) in doses >30 mg/kg/day or valproate (VPA) >60 mg/kg/day; (*iii*) *Normal dose polytherapy* - where multiple drugs were used, the doses being within accepted range; (*iv*) *High dose polytherapy* –where multiple drugs were used, of which at least 1 was in high doses as given above; and (*v*) *Change of drug* – change of a single drug to another single drug at therapeutic doses. Patients on polytherapy where a drug was changed were put under polytherapy as above. Though several strategies were used in most patients, that which was most effective in an individual patient and which was usually the one employed at study end, was the one considered for correlation with response.

Responses were classified into 4 groups. A complete or virtually complete response, allowing for an occasional breakthrough seizure, present for at least 3 months of follow up was called *full response* (*FR*). Patients with a marked and dramatic reduction in frequency and intensity of seizures or a documented numerical decrease in seizure frequency to <50% of initial frequency were labeled as *partial response plus* (*PR*+). Any reduction less than this was considered

partial response (PR). No change or worsening of seizures was called *no response (NR)*.

Results

Males predominated in the ratio of 2.2:1. Most patients (71%) had their first seizure before 2 years of age, with 53.6% before the age of 1 year. A family history was present in 13%. Very frequent/daily seizures were seen in 74%, with an additional 7% being in non-convulsive status. Mixed seizures were the most frequent (41%), followed by secondary generalized tonic clonic (SGTC) (20%), complex partial (CPS) (16%), myoclonic (14%), and simple partial (3%). As shown in *Fig. 1*, mixed and myoclonic seizure types were associated with severe MR, and SGTC and CPS correlates with normal or borderline mental functions. Most patients had static CNS disease (63%), with progressive disease and idiopathic epilepsy seen in just 17% each. The majority of patients did not fit into an identifiable syndrome. Syndromes seen included Lennox Gastaut (LGS) (18%), infantile spasms (IS) (14%), Kojheknikow's syndrome (5%) and frontal lobe CPS (5%).

Neurological abnormalities were present in 52%, equivocal findings in 11 and 36% were normal. A large number had some degree of MR (71%), ranging from borderline (8%), mild (12%), moderate (21%), to severe (30%).

EEG recordings were carried out in 88 cnildren and showed a high degree of correlation with the clinical type of seizure (81%). It should be noted that a normal EEG was present in only 16%. CT scan and MRI were done in 70 and 20 patients, respectively. They were helpful in the diagnosis in 38% and 48%, and in therapy decisions in just 7% and 16%, respectively. On analysis of the prior treatment given, 61% were on polytherapy with no benefit. Suboptimal dosages of antiepileptic drugs (AEDs) were being used in 78%.

Among the 100 cases with adequate follow-up, the mean duration was 18.45 months. Monotherapy was effective in achieving FR/PR+ in many patients (*Fig.2*); the majority of cases in the NR/PR group were on polytherapy. Overall a good response was seen in 67% (35% FR, 3% PR+), while a poor response was present in 33% (22% PR, 11% NR). On correlating response pattern to mental status and underlying disease (*Fig. 3*), a good response was more likely with nil or borderline MR and idiopathic disease. Conversely, severe MR was associated with a poor response. Static and progressive disease were associated with heterogenous responses. In the poor responders, abnoral CNS findings, 75% had a good response.

Adverse drug reactions were seen in

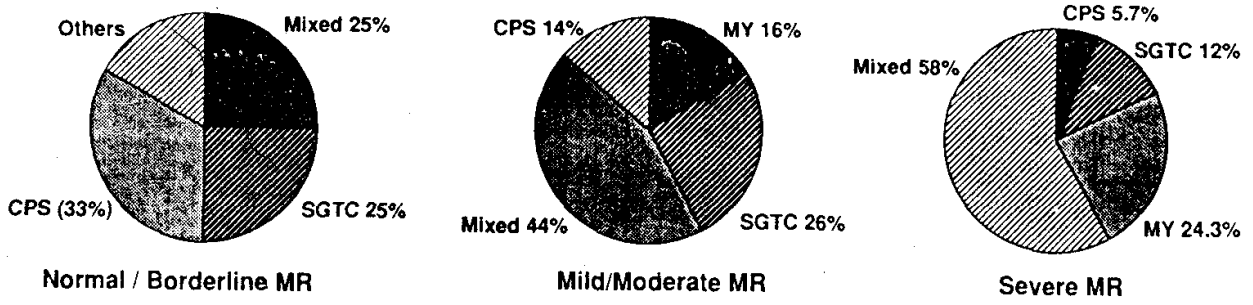

Fig. 1. Correlation of seizure type with MR.

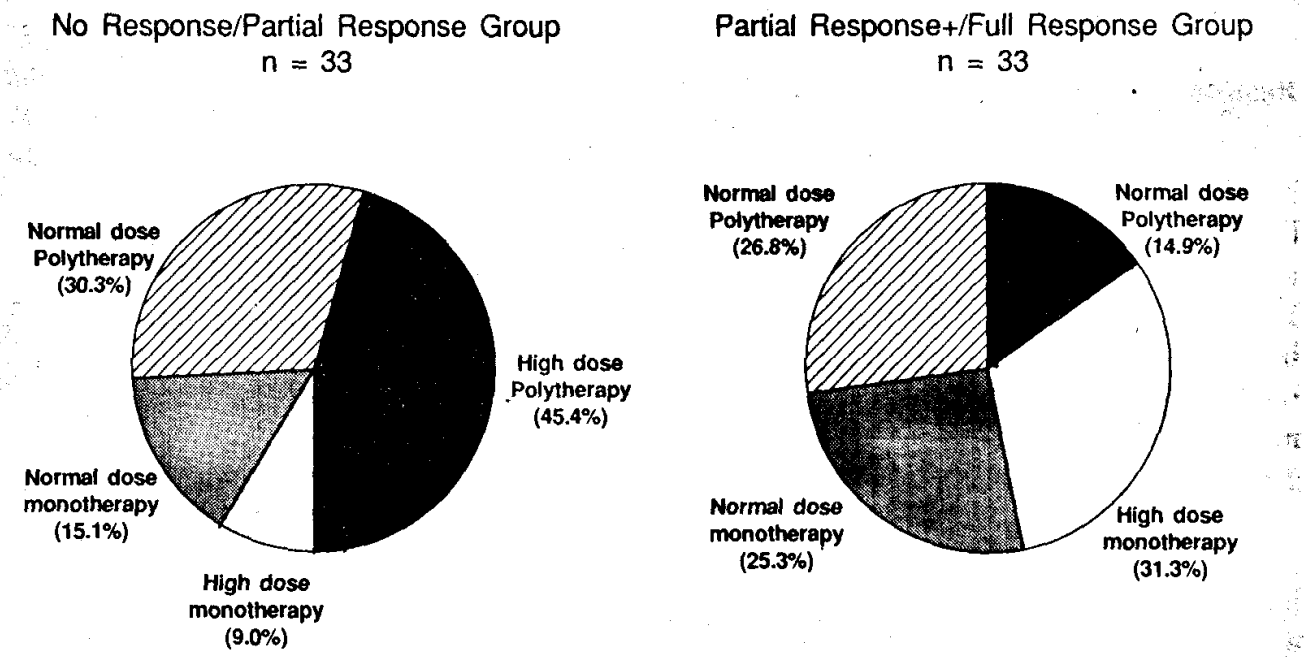

Fig. 2. Correlation of Strategies used versus response

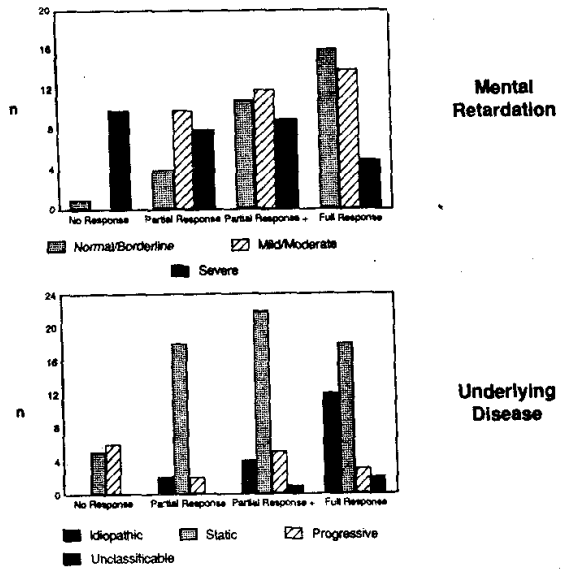

Fig. 3. Correlation of MR and underlying-disease with response.

41% but only in 6% were they life threatening and one case succumbed. CBZ and VPA, being the most commonly used drugs were the most frequent offenders, though no drug was free of side effects. Reactions seen with CBZ included ataxia, drowsiness, exacerbation of seizures, GI symptoms and a single case of idiosyncratic thrombocytopenia. Anorexia and vomiting were the commonest side effects of VPA, followed by hepatitis (seen in 6 cases), thrombocytopenia and drowsiness. Mortality in our series was 4%, with one child dying of VPA induced toxic hepatitis and the others due to uncontrolled seizures.

Discussion

True intractable epilepsy would necessitate a trial of all possible drugs in an adequate dosage (with confirmation of compliance by drug levels), for a prolonged period of time, *i.e.*, 2-3 years. Though such a definition is ideal for pre-surgical selection it would miss many difficult to control epileptic children in clinical practice. Livingstone(3) has defined intractable epilespy as that "epilepsy that is not controlled by first line conventional antiepileptic drugs". His definition is broad and would include all cases of difficult to control epilepsy. We have, therefore, used a similar though not identical definition of what we have called difficult to

control epilepsy. On analysis of the risk factors associated with DCE in our 123 cases, a certain clinical picture emerged. The intractable epileptic was more likely to be a male, with an age of onset of seizures below 2 years, with evidence of either static or progressive neurological disease, in the form of mental retardation/regression, and/or abnormal neurological findings. He would also be more likely to have myoclonic, SGTC, CPS or a mixture of the seizure types. Finally, he might also fit into known epileptic syndromes, especially Lennox Gastuat, West or Kojheknikow's syndromes.

The male predominance in our series is unlikely to be due to a social bias against girl children, as this is an extremely disruptive disorder unlikely to be left untreated. In addition, Aicardi(4) and Rodin(5) have also found a male preponderance among their epileptics. They may be due to the fact that MR is known to be higher in males, and MR itself was a risk factor in our patients.

Several workers have confirmed that age of onset of seizures less than 2-3 years is a significant risk factor for refractoriness(6,8). Huttenlocher(6) found that 70% of his retarded cases had an onset of epilepsy <2 years of age. In comparing 'mild' epileptics with 'moderate to severe' epileptics, Roger found that in the latter group, 38-53% had on onset <3 years, as compared to 0-20% in the former(7). In the only study which looked at newly diagnosed epileptics followed up for 8 years prospectively, among the 22% who were refractory to treatment, age of onset was not an independent risk factor(9). It is, therefore, possible that as the age of onset in mentally retarded children is less than 2 years in the majority, this and not the age of onset, is the primary risk factor. In our series, 62% of cases had MR and 63% had abnormal/equivocal CNS findings which has been noted by other authors also(4,5).

In our series, the bulk, of cases had a mixed type of seizure disorder (41%), which included myoclonic, atonic, partial and SGTC. A significant percentage had either partial seizures or partial with secondary generalization (36.5%). A sizeable number (13.8%) had pure myoclonic epilepsy. This is in accordance with several studies who have found partial or mixed seizures to have the worst prognosis(5,7). Only 10-18% of CPS go into remission and it is apparent that complex partial seizures were worse than simple partial(7). Certain types of CPS are more prone to intractability, *i.e.*, reflex triggered (startle) or frontal lobe complex partial (FLCPS) with drop attacks(7). In our patients, 6 had FLCPS and 3 had reflex triggered seizures. It is important to realize that PGTC, simple absence and simple partial seizures (excluding epilepsia partialis continua–EPC) were hardly ever seen in our series, as well in other series. In trying to see the correlation between seizure type and MR, it was observed that 80% of mixed seizure patients and 94% of those with myocolonic seziures had MR, most of them severe. In comparison, normal or borderline IQ was seen in 65% of CPS and 40% of SGTC. It is evident that CPS and SGTC may be independent risk factors for intractability.

Positive family history (FH) as an adverse prognostic factor was not found by us as only 16% had this. This has to be interpreted with caution, however, as epilepsy in the family is considered a stigma in Indian social conditions, and this history may not be forthcoming. In western retrospective series, divergent views have been expressed(7,8). In the only prospective study in newly diagnosed epileptics, family history was not an adverse prognostic factor for refractoriness(9). Symptomatic epilepsies

which formed the bulk of our cases are usually not genetic, which explains our low incidence of positive FH.

From our data, it became apparent that normal or non-specific abnormalities on EEG were distinctly unusual in DCE, seen in only 16 and 3%, respectively. These appear to be almost identical figures to Grover *et al.*(10) whose study of chronic seizures in children showed 19% EEGs to be normal. When we correlated EEGs with seizure types, it became clear that in four out of every five patients, the EEG helped in confirming the seizure type. This is in agreement with previous reports(7). In contrast, when considering all types of epilepsy, consistent EEG abnormalities occur in only 35-65% of cases(11,12). If the EEG is normal consistently one must consider other non-epileptic paroxysmal disorders in the differential diagnosis.

CT and MRI results were disappointing in our series. Though abnormalities were found in 38-48% of our cases, in only 7-16% did they lead to a change in therapy. It can be concluded with reasonable certainty, from both ours and others' results that neuroimaging is inferior to EEG in both confirming seizure disorder and in therapeutic adjustments. Chadwick found only 10% of CT lesions to be treatable(11). It must be kept in mind that 95% of patients with an abnormality on CT had abnormal focal EEGs as well(12). Hence, the EEG, if focally abnormal, could be used as a first line investigation to decide whether the more expensive neuroimaging be pursued.

The best treatment modality for truly intractable epilepsy is surgery. In our setting, without the requisite sophisticated evaluation techniques this approach is not yet feasible. No ideal medical treatment strategy exists, which explains the plethora of different regimens and combinations tried. We used five basic treatment regimes in our patients, often sequentially and only the best strategy response was analysed. A simple change of drug was the least effective, achieving a response in only 1 patient. Elwes(9) and Brodie(13) both found that if the first line of therapy was ineffective, the likelihood of a response to the second line of therapy was poor. The most successful regimens we found were normal or high dose monotherapy, where it gave a full response in 84% of those maintained on those regimens. Most of these patients had either been switched from polytherapy to monotherapy, or the dose has been stepped up. Schmidt(14), Lesser(15) and Reynolds(16) have found that between 53-83% of patients have either a reduction in seizures, or remained the same, without adverse effects, with a change from polytherapy to monotherapy. One of the reasons postulated for this reduction in frequency is that sedative anticonvulsants drugs were withdrawn(3). Certain types of seizures are exacerbated by CBZ, *e.g.*, atonic, myoclonic, GTC and frontal lobe partial(17). This was seen by us in 10 cases.

In our series, 21/24 were effectively controlled with high dose monotherapy, especially sodium valproate. Drug dosages of 80-100 mg/kg/day were often used, with drug levels frequently exceeding so called 'normal' therapeutic range. In a study of 25 children by Hurst(18), this expanded therapeutic range of VPA was emphasized where levels were between 119-196 mcg/ml. In his series, 70% of those on high dose VPA as monotherapy showed a full response, whereas only 11% on high dose VPA as part of polytherapy responded fully.

Polytherapy in normal or high dosage achieved a full or good response in only 53%

of patients maintained on these regimens. A possible reason for the poor results was the fact that this group of patients probably had more severe seizures, and it was impossible at times to switch them to monotherapy. Similar results have been reported by several authors(13,15). It is likely that a small group of patients benefit from the addition of a second drug, as shown by Schmidt(14), especially when the drugs have different mechanisms of action and may synergize.

Though adverse effects occurred in a significant number of cases (41%), these are to be expected in a bad disease like DCE, both because of high dosage requirements and polytherapy. Schmidt found that the adverse drug reaction (ADR) rate with monotherapy was 27%, which increased to 38% with polytherapy(14). We used CBZ and VPA maximally as CBZ and normal dose VPA have virtually no cognitive side effects(19). Though the number of hepatitis cases appeared to be high, only 2 out of the 6 were clearly toxic hepatitis, while the other 4 could have been viral.

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NOTES AND NEWS

IV ANNUAL CONFERENCE IAP HARYANA STATE BRANCH

The IV Annual Conference of Haryana State Branch of IAP is to be held on *19 December, 1993*. The conference will be hosted by the IAP Faridabad Branch at Hotel Delite.

The last date for submission of Scientific Papers with Abstract is 31 October, 1993. It should accompany Registration fee of Rs. 125/- as D/D in name of 'IV Annual Conference FBD Haryana'.

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