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Original Research Article

Understanding the enigma of neurobehavior in children with epilepsy and the need for mandatory screening: a prospective case control study

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ABSTRACT

Background: In epilepsy management, control of seizures is the prime objective and reduction in seizure frequency is the main goal for successful treatment. There is a high prevalence of neurobehavioral problem. Hence, there is a need to screen, and intervene. Aim was to identify the neurobehavioral profile and the impact on children with epilepsy
Methods: After IRB clearance, 100 consecutive school-aged children 4-17 years with normal IQ attending epilepsy clinic were enrolled as cases, and 102 age, gender and socio-economic status-matched children without epilepsy were chosen as controls. The strength and difficulties questionnaire are administered to both groups. It addresses five domains: emotional, conduct, hyperactivity, and peer problems which contribute to the total difficulties score, and fifth dimension prosocial behaviour.
Results: Among the children with epilepsy, emotional issues were observed in 41%, conduct issues in 67%, hyperactivity behaviour in 54%, and peer problems in 64% while pro-social behaviour was only 27%, and total difficulty score was 60%, which was statistically significant with $p<0.001$ in all domains when compared to control. The impact of the disease was 73%, home environment was affected in 67%, classroom learning 45%, 28% in leisure activities, and 10% in friendship, which was statistically significant with $p<0.001$ in all domains when compared to control.
Conclusions: We have identified emotional, conduct, hyperactivity and peer problems having significant impact on children with epilepsy. Hence a screening in various behavioural domains helps in early identification and prompt intervention of neurobehavior.

Keywords: Epilepsy, Behaviour, Comorbidity, Strength difficulty questionnaire

INTRODUCTION

Epilepsy is a common medical condition found in children worldwide from ancient times.[1,2] The burden of epilepsy is especially huge in developing countries in south east Asia, Africa, South America.[3,4] The incidence is 86 per 1,00,000 persons. It is an electrical neuro-disorder of brain. Though recurrent seizure is the hallmark of epilepsy, there can be wide variance from blankness to gross jerky movements of hands, feet and jaw. The episode of seizure is brief lasting few seconds to few minutes. After the seizure episode the child reverts to normality. The frequency of seizure variable from once in a year to once in a week.[5-7] Over the years, there have been tremendous improvement in reporting, diagnosis and treatment of epilepsy with 80% response for antiseizure medication ASM. As the children grow older the disorder shows spontaneous remission in certain percentage. There have been systematic, cohort studies on childhood epilepsy over several years with focus on

natural history and seizure containment.[8-11] The epilepsy affected children live longer, have achieved good positions in education, arts, science, music, sports, politics and performing arts. Since growth and development are integral for children, seizure disorder, chronic, ictal, spanning some years, how will it impact development into responsible humans? How do the suffering child perceive the seizure attach, how do the parents respond and support the child, how do the neighbourhood families influence, has considerable influence on the behaviour. That's how several studies took up research on behavioural aspects in children with epilepsy. They have used their own convenient questionnaire tool collecting information on behaviour from parents, siblings and affected individuals. There are over 114 questionnaire tools available. The literature is full with- small cluster studies, large population studies and systematic review studies. The results are inconclusive, suffer from systemic bias, emotional overtones and suggest additional work. These studies also ponder psycho-behaviour and epilepsy impact each other. The neurobehavioral comorbidities observed in children with epilepsy (CWE) are resultant of a number of factors like genetic, birth injury, congenital abnormality, asphyxia and infections.

In India too, childhood epilepsy is one of the most common neurological conditions. It is estimated that prevalence is 5.59 cases per 1,000 children.[12] In the studies conducted earlier, the prevalence of psychopathology in CWE is found to be 16-77%.[13] Such behaviour disabilities can impact learning, motor skills, scholastic performance and performing arts. Hence their early identification is crucial along with antiseizure measures.[14] The primary objective of our study is to identify the neurobehavioral profile in children with epilepsy and its impact on various areas of life when compared to children without epilepsy. There are various scales available for behavioural assessment in children. We have selected strength difficulty questionnaire. The Strength and Difficulty Questionnaire (SDQ) is in use for a long time. It is used widely all over the world for assessment of behaviour disorder. It is free, easily accessible, validated, easy to administer tool. Also, this tool has been of use in wide range of age group (2-17 years).[15] The SDQ has shown its use in Indian studies. It shows good psychometric properties in different socio-cultural settings.[16,17]

METHODS

Study setting and design

Study done at Indira Gandhi Institute of Child Health, Bangalore, during January to June, 2023. This is prospective, questionnaire based, observational, case-control study, conducted at a tertiary care government hospital in Bangalore over a period of 6 months. We adhered to all the protocols of research studies concerning human beings. The study objectives are explained to the parents of children. Informed written consent obtained from the primary caregivers of the participants before their inclusion into the study

Inclusion criteria

Every consecutive child/adolescent attending the epilepsy clinic and diagnosed with epilepsy with normal IQ was included. The inclusion criteria are as follows: Children aged 4-17 years and duration of epilepsy of at least 6 months. Controls were recruited from the paediatric OPD for routine health check-ups and vaccination.

Exclusion criteria

The children with neurodevelopmental disabilities like autism spectrum disorders, cerebral palsy, psychiatric illness or other chronic diseases were excluded from both groups.

Sample size estimation

The prevalence of behavioural comorbidity in children with epilepsy is varied, with some showing rates as high as 53%. To achieve an expected prevalence of 50% behavioural comorbidity in our study, with a 95% confidence level and a±0.10 width of confidence (CI), we calculated that a sample size of 96 patients would be required.

Case definitions for study enrolment

We have adhered to standard definitions concerning Epilepsy, Epilepsy control, Drug resistant epilepsy, School dropout and Irregular school attendance, in our study use.

Evaluation tools

All patients, underwent the vineland social maturity scale (VSMS) for IQ assessment and those with scores above 70 were enrolled. All cases and controls were administered a linguistically appropriate questionnaire, the Strength and Difficulties Questionnaire (SDQ) to screen for neurobehavioral disorders. The SDQ parent's version was administered, focusing on 5 domains: hyperactivity, emotional, conduct, peer problem and prosocial behaviour. It screened children with neurobehavioral disorders by measuring the total difficulties, individual symptom scores and total impact scores. A total difficulties score was generated by summing scores from 4 domains, except the prosocial domain. A total difficulty score of 0-13 was considered close to average, 14-16 was slightly raised, 17-19 was high, and 20-40 very high. An additional supplement was used to assess the impact of neurobehavioral problems on home life, peer relationships, classroom learning, leisure activities, and overall distress. The internal consistency of the tool was 0.73, the test-retest reliability was 0.62, and the sensitivity and specificity of the scale were 95% and

35% respectively. The data so collected is anonymous and fully confidential.

Statistical analysis

Data were analysed using R software Version 4.1.1, R Core Team (2021). All categorical data were presented using frequency and percentages, and all continuous data were described using mean±SD or Median and interquartile range based on the distribution. The baseline demographics, clinical, and developmental parameters were compared by Epilepsy status and SDQ using the Chi-square test or Fisher's exact test based on the expected frequency. The p value was considered significant at 5% level of significance.

RESULTS

Socio-demographic factors

The mean (SD) age of children with epilepsy (cases) and children without epilepsy (control) is 8.97 (3.82) and 9.3 (3.55) with male to female ratio of 1.5:1 and 1.2:1 respectively. A majority of children are from a lower socioeconomic class (Modified Kuppuswamy scale) in both groups. Both groups are age, gender and SES matched.

Table 1: Distribution of cases and control based on gender.

Sex	Groups, N (%)		Total	P value
	Epilepsy	Control		
Female	39 (39.0)	46 (45.1)	85 (42.1)	0.38
Male	61 (61.0)	56 (54.9)	117 (57.9)	
Total	100 (100)	102 (100)	202 (100)	

Table 2: Age wise distribution.

Age (years)	Groups, N (%)		Total	P value
	Epilepsy	Control		
≤10	63 (63.0)	62 (60.7)	125 (61.8)	0.746
11-18	37 (37.0)	40 (39.2)	77 (38.1)	
Total	100 (100)	102 (100)	202 (100)	

Clinical characteristics

Children with epilepsy are irregular in school attendance (30%), learning issues (24%) and behavioural (21%) compared to children without epilepsy, where the percentages were 7%, 1%, 5% respectively (p<0.001). School dropout is observed in 5% of cases while none occurred in the control group.

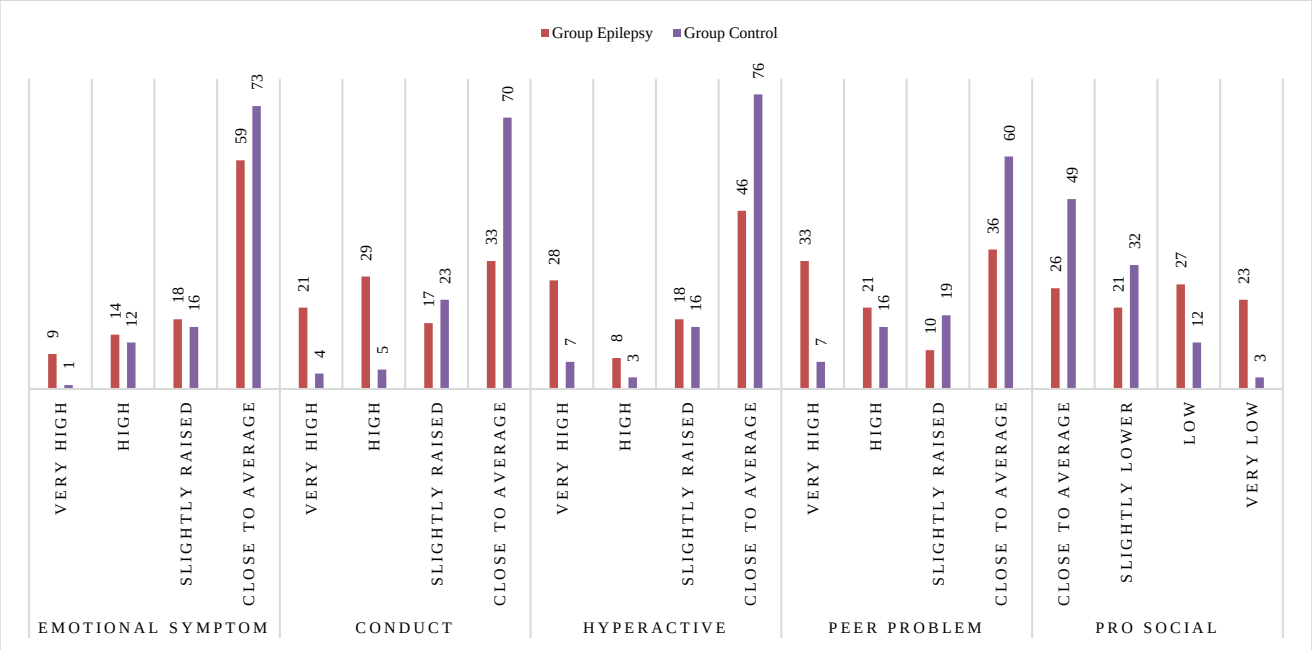

Figure 1: The behavioural profile in various domains using the SDQ questionnaire.

Epilepsy-related variables

It was noticed that 66% are on monotherapy, and 34% are on polytherapy. Among the children on monotherapy, 18.2% had very high scores compared to 61.8% among those on polytherapy. The majority are on treatment with levetiracetam 71%, and the second most commonly used drug is sodium valproate 17%. Seizure control is observed in 64%, while 36% had poor seizure control. Drug resistance is seen in 15% of cases. This study found that children on polytherapy, those with uncontrolled seizure and drug-resistant cases exhibited significant behavioural changes compared to those on monotherapy, well-controlled and drug-responsive cases (p<0.001). There are no significant differences in the total difficulty

score between children with focal seizures and those with generalized seizures.

Behavioural comorbidities

In children with epilepsy, 40% had close to average scores, 12% had slightly raised scores, 15% had high scores, and 33% had very high scores. In children without epilepsy, 68.6% had close to average, 15.7% had slightly raised scores, 7.8% had high scores, and 7.8% had very high scores. This difference is statistically significant with p<0.001. The behavioural profiles in various individual domains are presented in (Table 2). The p value was significant in all the individual domains.

In our study, among the cases, of children with epilepsy (group 1) 39 (39%) were females, 61 (61%) were male, the control group (group 2), 46 (45.1%) were female and 56 (54.9%) were males. The ratio of male to female among cases was 1.56:1 and among controls was 1.21:1. The difference in proportions was not statistically significant (p=0.38).

Table 3: Distribution based on socioeconomic status.

Socioeconomic status	Groups, N (%)		Total	P value
	Epilepsy	Control		
Lower upper	74 (74.0)	71 (69.6)	145 (71.8)	0.786
Middle lower	21 (21.0)	25 (24.5)	46 (22.8)	
Upper middle	5 (5.0)	6 (5.9)	11 (5.4)	
Total	100 (100.0)	102 (100.0)	202 (100.0)	

Table 4: Distribution based on the behavioural problems seen in children with epilepsy compared to children without epilepsy based on history.

Behaviour problem	Groups, N (%)		Total	P value
	Epilepsy	Control		
Yes	21 (21.0)	5 (4.9)	26 (12.9)	0.001
No	79 (79.0)	97 (95.1)	176 (87.1)	
Total	100 (100.0)	102 (100.0)	202 (100.0)	

Table 5: The classification of epilepsy based on the etiology.

Etiological classification	SDQ TDS, N (%)				Total	P value
	Very high	High	Slightly raised	Close to average		
Electroclinical syndrome	20 (30.8)	10 (15.4)	8 (12.3)	27 (41.5)	65 (100.0)	0.714
Structural epilepsy	9 (31.0)	4 (13.8)	4 (13.8)	12 (41.4)	29 (100.0)	
Unknown epilepsy	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	2 (100.0)	
Immune-mediated	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	
Infectious	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	
Total	33 (33.0)	15 (15.0)	12 (12.0)	40 (40.0)	100 (100.0)	

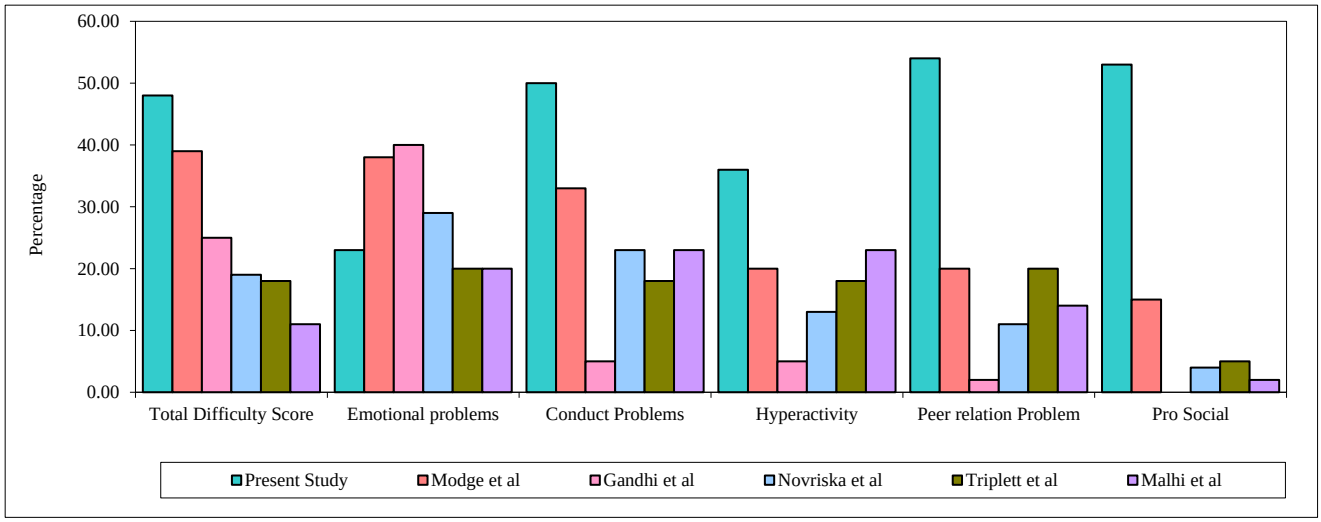

Figure 2: Comparison of various studies using SDQ for co-morbidities in CWE.

Based on age group, further divided into less than 10 years, and adolescent group 11-18 years. Among less than 10 years 63 (63%) had epilepsy and 62 (60.7%) were non-epileptics.

In the adolescent group 37 (37%) among epileptics, and 40 (39.2%) among non-epileptics. The p value was 0.746 which is not significant. As our study was conducted in a tertiary referral government hospital, the majority of patients in both groups belonged to lower upper socioeconomic status according to modified Kuppuswamy's classification. In our study population of 100 cases and 102 control, it was found that age distribution, gender, and Socioeconomic structure, i.e. baseline demographic data were similar and cases and controls were from the same cohort. The p value was not statistically significant in all of the above. Epilepsy was further classified based on the aetiology. The majority of the cases were electroclinical syndrome, the second most common seen was structural-metabolic. The p value of 0.714 suggests there was no significant difference in the SDQ score among various types of epilepsy.

Impact of behavioural problem

The impact was scored as 0 for not at all and a little, 1 for quite a lot and 2 for a great deal. The total impact score was calculated by summing up all the 5 domains. The (Table 2) shows the impact in various areas among cases and control.

Table 6: Comparison between the subscale of SDQ in CWE compared to children without epilepsy.

Domains		Children with epilepsy (n=100)	Children without epilepsy (n=102)	P value
SDQ TDS	Very high	33 (33.0)	8 (7.8)	<0.001
	High	15 (15.0)	8 (7.8)	
	Slightly raised	12 (12.0)	16 (15.7)	
	Close to average	40 (40.0)	70 (68.6)	
Emotional symptom	Very high	9 (9.0)	1 (1.0)	0.043
	High	14 (14.0)	12 (11.8)	
	Slightly raised	18 (18.0)	16 (15.7)	
	Close to average	59 (59.0)	73 (71.6)	
Conduct	Very high	21 (21.0)	4 (3.9)	<0.001
	High	29 (29.0)	5 (4.9)	
	Slightly raised	17 (17.0)	23 (22.5)	
	Close to average	33 (33.0)	70 (68.6)	
Hyperactive	Very high	28 (28.0)	7 (6.9)	<0.001
	High	8 (8.0)	3 (2.9)	
	Slightly raised	18 (18.0)	16 (15.7)	
	Close to average	46 (46.0)	76 (74.5)	
Peer problem	Very high	33 (33.0)	7 (6.9)	<0.001
	High	21 (21.0)	16 (15.7)	
	Slightly raised	10 (10.0)	19 (18.6)	
	Close to average	36 (36.0)	60 (58.8)	
Pro-social	Close to average	26 (26.0)	49 (48.0)	<0.001
	Slightly lower	21 (21.0)	38 (37.2)	
	Low	28 (28.0)	12 (11.8)	
	Very low	25 (25.0)	3 (2.9)	

Table 7: Showing the impact on various areas of life in CWE compared to children without epilepsy.

Variables		Children with epilepsy (n=100)	Children without epilepsy (n=102)	P value
Upset/distress child	Great deal	9 (9.0)	0 (0.0)	<0.001
	Medium amount	14 (14.0)	1 (1.0)	
	A little	63 (63.0)	0 (0.0)	
	Not at all	14 (14.0)	101 (99.0)	
Home life	Great deal	28 (28.0)	0 (0.0)	<0.001
	Medium amount	39 (39.0)	6 (5.9)	
	A little	27 (27.0)	0 (0.0)	
	Not at all	6 (6.0)	96 (94.1)	

Continued.

Variables		Children with epilepsy (n=100)	Children without epilepsy (n=102)	P value
Friendship/peer relations	Great deal	10 (10.0)	0 (0.0)	<0.001
	Medium amount	21 (21.0)	2 (2.0)	
	A little	48 (48.0)	0 (0.0)	
	Not at all	21 (21.0)	100 (98.0)	
Classroom learning	Great deal	23 (23.0)	0 (0.0)	<0.001
	Medium amount	22 (22.0)	3 (2.9)	
	A little	43 (43.0)	0 (0.0)	
	Not at all	12 (12.0)	99 (97.1)	
Leisure activity	Great deal	5 (5.0)	0 (0.0)	<0.001
	Medium amount	23 (23.0)	0 (0.0)	
	A little	41 (41.0)	0 (0.0)	
	Not at all	31 (31.0)	102 (100.0)	
Total impact score	Very high	38 (38.0)	0 (0.0)	<0.001
	High	16 (16.0)	12 (11.7)	
	Slightly raised	19 (19.0)	0 (0.0)	
	Close to average	27 (27.0)	90 (88.23)	

DISCUSSION

In this study, the prevalence of neurobehavioral problems in children with epilepsy is 48% compared to 16% in children without epilepsy.

Indian data from Mumbai, Maharashtra showed a prevalence of 39.1% among CWE and 7.9% among normal children.[18,19] Choudhary et al from Delhi documented a prevalence of 43%,[20,21] while a hospital-based study from Southern India reported a much higher prevalence of psychopathology of 53.8%.[22] Emotional symptoms are observed in 23%, conduct problems in 50%, hyperactive behaviour in 36%, peer problems in 54% and reduced pro-social behaviour was seen in 53%. In a study done by Anita et al emotional problems are noted in 38%, conduct problems in 32%, hyperactivity behaviour in 44%, peer problems in 38% and reduced pro-social behaviour in 15%.[8] The higher prevalence of peer problems reduced prosocial behaviour, in the current cohort may be attributed to a lack of schooling and socialization during the pandemic in addition to their epilepsy-related peer problem. Secondly might also be attributed to disrupted child and family routines and reduced socialization due to disease stigma. The impact of neurobehavioral problems is significant in children with epilepsy when compared to children without epilepsy. It is found to affect home life (28%), classroom learning (23%), distressed child (9%), friendship/peer relationship (10%), and leisure activity (5%). The p value is significant (p<0.001) in all domains. The SDQ questionnaire helps identify the needs of the person beyond the diagnosis and severity of epilepsy. Epilepsy treatment strategies continue to focus on the clinical aspects, but holistic care needs to address both clinical symptoms and social aspects. The externalizing score is calculated by summing the hyperactive behaviour score and conduct problem score. The internalizing score was calculated as the sum of the emotional score and peer problem score. In this study, the externalizing disorder is more commonly observed than the internalizing disorder. Mishra et al study observed that externalizing behaviour is common in younger children and both internalizing and externalizing behaviour in older age groups.[9] In a study done by Anita et al, internalizing disorder is more commonly observed than externalizing. In their study, the majority are adolescents, while in the present study majority are less than ten years old. We have looked into 6 studies using SDQ as the measuring tool. All these studies conducted in reputed tertiary care teaching hospitals, sample size lowest 47 to 222 highest, using SDQ, have inherent strength and weakness in presentation of results.

There are only two studies that mention uniform, clear results. The prevalence of behaviour problem in CWE varies from 11% to 48%. The results highlight emotional, Conduct, Peer relation problems and Hyperactivity in CWE, while our study show lower score for Emotional problems and Gandhi et al show less of Hyperactive problems. This is due to sample of participants being children, use of SDQ-P or SDQ-S, mindset of participants, projection towards illness, cultural background, access to support system, their responses are bound to vary and are natural expressions in the complex milieu. Tanabe et al find very high percentage of behaviour problems specially hyperactivity and conduct problems, Novriska et al in their sample more of female children, adolescents, participants drawn from upper and lower economic groups find modest difficulty scores, Triplett et al in their adolescent children, again find a modest difficulty score, Modge et al in a very detailed informative study with fairly large sample size, participants from low income group, half of the CWE show structural abnormalities in brain, have learning problems, school dropouts, find fairly high difficulty score, Gandhi et al smallest sample size, used SDQ-S, adolescent children, find moderate difficulty score, Berg AT et al simple cursory study, adolescent children find very modest difficulty score.[23-27] Now searching from

historical perspective, there are number of studies in the last two decades, using Child Behaviour Check List (CBCL) to screen the behavioural problems in children. Datta et al 2005 study, information collected through parents, sample size 132 children, report CWE have 53.8% behavioural problems. The CBCL consists of 118 behaviour problem items on which caregivers rate their children. Suggest for a simple tool for assessment of behaviour. Choudhury et al 2008 study, sample size 100 children, predominantly male children, observational study, report 43% behaviour problems in CWE. Misra et al 2015 in their study, information collected through parents, 240 children sample size, equal representation of male/female gender, children/ adolescents report mean values of behavioural scores in patients with epilepsy, are significantly higher as compared to control in all domains of emotional reactivity, withdrawn, attention problems, aggressive behaviour externalizing and total behaviour problems. Then earliest studies, quite good number, using many other questionnaires like Structured Psychiatric interview, Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), Diagnostic Interview Schedule for Children, parent questionnaires to reach a psychiatric diagnosis, symptom-based standardized parent, teacher, or child self-report questionnaires

Table 8: Comparison of SDQ Scores in different studies concerning CWE.

Parameters	Present study (%)	Anita et al[20] (%)	Gandhi et al[24] (%)	Novriska et al[23] (%)	Triplett et al[25] (%)	Berg AT et al[27] (%)
Total difficulty score	48	39	25	19	18	11
Emotional	23	38	40	29	20	20
Conduct	50	33	5	23	18	23
Hyperactivity	36	20	5	13	18	23
Peer relation	54	20	2	11	20	14
Prosocial	53	15	0	4	5	2

Berg et al is a review study, highlight, natural responses to chronic disease like epilepsy in context of community, the systemic bias in parent reported child behaviour, understanding Psychogenic non-epileptic seizures and a need for balanced approach.[28] Austin et al a meta-analytical study, bring out importance of chronicity of epilepsy, family environment, socio-cultural aspects in community and access to support system, looking also into psychotic elements influencing behaviour. Also find ASM, polytherapy may also cause behavioural problems.[29-33] Holmes et al in his important articles, mention, importance of causative for epilepsy impacting cognitive skills and highlight insufficient clinical data.[32,33] Eddy et al in their article have stressed the importance of ASM, specially be responsible for behavioural disorder.[33]

Mula et al 2021 a review study, finds one in three CWE has behavioural comorbidity, casualty uncertain, then antipsychotic treatment regimen a question to be answered.[34] Wei et al In their article about identifying the epilepsy related comorbidities in the early stages and such screening should be an integral part of management of epilepsy.[35] That's how looking through the lens of several researchers, over 100 years, using time related screening tool, some small cross-sectional studies, others community based large observational studies, have come out with the understanding that behavioural problems are part of CWE in varying percentage, their association is well established but casualty is still a large issue to be searched.[35] In our opinion, SDQ as scoring tool, used in studies all over the world in large number of occasions can be a good decider. A last concern that comes to mind is, what is the treatment regimen for Psychoneurotic-behavioural problem?

Limitations

Using teacher's and self-questionnaire in addition to the parent's questionnaire would have provided a better understanding of the child's behaviour. Long-term follow-up and periodic reassessment of behaviour could not be conducted. The study population consisted of hospital-referred children, making it difficult to generalize the results to the general population.

CONCLUSION

We have identified the prevalence of externalizing and internalizing behaviour problems in CWE compared to children without epilepsy. Peer relation problem was the most significant neurobehavioral issue, impacting on friendship and family life. Therefore, behavioural assessment should be a part of standard care to ameliorate their inclusiveness in society.

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