

ASSESSMENT OF NEUROPSYCHIATRIC COMORBIDITIES IN EGYPTIAN CHILDREN WITH EPILEPSY USING THE MINI-KID TOOL

By

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ABSTRACT

Background: Epilepsy is considered as one of the most common neurological diseases in children with an increased risk of multiple comorbidities.

Aim of the Work: The aim of this study is to determine the frequency of neuropsychiatric comorbidities in children with epilepsy & analyze the association between neuropsychiatric comorbidities in children with epilepsy with several risk factors.

Subjects & Methods: Mini International Neuropsychiatric Interview for children and adolescents (MINI-KID) (child version) was used to assess the neuropsychiatric disorders of 100 children with epilepsy (CWE) and 100 healthy children from the outpatient clinic and inpatient neurology unit of pediatric department of Al-Zahraa-university hospital. In addition, Vanderbilt Attention-Deficit Hyperactivity Disorder Diagnostic Parent Rating Scale (VADPRS) was used for confirming the diagnosis of Attention Deficit Hyperactivity Disorder (ADHD). Socio-demographic and clinical data were collected through detailed history taking from parents.

Results: CWE had a significantly higher frequency of neuropsychiatric disorders (65%) compared to healthy control children (38%), 24% of CWE had multiple neuropsychiatric disorders compared to 10% in control group ($p = <0.001$). The younger the age at seizure onset ($p=0.043$), the longer the duration of epilepsy ($p=0.017$), the focal seizure ($p=0.002$), focal epilepsy type ($p=0.003$) and presence of environmental risk factors ($p=0.005$) the more the neuropsychiatric disorders among children with epilepsy.

Conclusion: Neuropsychiatric disorders are more common in children with epilepsy. Regular screening of children with epilepsy for neuropsychiatric comorbidities and health education programs for parents about the nature of the epilepsy disease and its comorbidities are highly recommended.

Keywords: Epilepsy, neuropsychiatric comorbidities, MINI-KID, Children.

INTRODUCTION

Epilepsy is considered as one of the most common neurological diseases, approximately 50 million people currently live with epilepsy worldwide, with an estimated 2.4 million people are diagnosed with it each year (WHO, 2018) and 0.9-2% of the pediatric population affected with it (Baumer et al., 2017).

Children with epilepsy experience not only seizures but also psychiatric and behavioral problems which have a great effect on their quality of life (Bilgiç et al., 2018).

Psychiatric disorders have long been studied in relation to epilepsy, providing a good evidence for its high prevalence in childhood epilepsy as compared to other chronic diseases (Besag et al., 2016). However, the relation between epilepsy related factors and psychiatric disorders remains unclear (Salpekar and Mula, 2018).

SUBJECTS AND METHODS

This is a cross sectional prospective comparative study conducted from May to November 2018 and carried out on 100 children with epilepsy and other 100 healthy children. Children were selected from outpatient clinic and inpatient neurology unit of pediatric department of Al-Zahraa

university hospital.

Inclusion criteria:

Inclusion criteria include children with age from 6-18 years. CWE were diagnosed according to international league against epilepsy (ILAE) 2014.

Exclusion criteria:

Exclusion criteria for CWE include children with other chronic diseases and history of intracranial operation within the past month, while for control group we exclude children with any chronic disease including epilepsy and other neurological disorders.

Ethical consideration:

- Well-informed verbal and written consents were obtained from one of the parents for every child before the study.
- Approval of the local ethical committee in the pediatrics department, college and university were obtained before the study.
- Written consents were obtained from the sectors of Al Azhar institutes.
- The authors declared no potential conflict of interest with respect to the research and publication of the article.
- All the data of the patients and

results of the study are confidential and the children have the right to keep it.

- The authors received no financial support for the research and publication of the article.

After obtaining well-informed consent from children's parents, socio-demographic and clinical data were collected through detailed history taking then the neuropsychiatric assessment was done through interviewing children with the Mini International Neuropsychiatric Interview (child version) and interviewing parents with Vanderbilt Attention-Deficit Hyperactivity Disorder Diagnostic Parent Rating Scale (VADPRS).

Instruments description:

1. The Mini International Neuropsychiatric Interview for children and adolescents (MINI-KID) (Child version). MINI-KID interview was designed on the basis of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and International Classification of Diseases 10th version (ICD-10). It's divided into diagnostic modules, each module includes both screening questions (except for psychotic disorders module) and diagnostic sections; the

diagnostic questions were asked only when the screen questions were positive. All questions were answered in a "yes or no" format (Sheehan et al., 1998).

The Arabic version of (MINI-KID) used in our study is approved to be valid (Ghanem et al., 1999).

2. (VADPRS) is a 45-item symptom scale which includes all 18 DSM-IV behaviors for ADHD, an 8 items for oppositional defiant disorder, a 12 items for conduct disorder, and a 7 items for anxiety and depression screen. The scale utilizes a 4-point scale from never (0) to very often (3) (Wolraich et., 2013), for diagnosis of any of these disorders symptoms must occur "often" or "very often" for at least past 6 months (American Psychiatric Association, 2013).

3. We used it in our study for confirmation of diagnosis of ADHD and determining its subtypes.

4. Statistical methods:

We used the statistical package SPSS (Statistical Package for the Social Sciences) version 25 for coding and entering data. For quantitative data, we summarized it using mean, standard deviation (SD), median, minimum and maximum, while for categorical data, frequency (count) and

relative frequency (percentage) were used. The non-parametric Mann-Whitney test was used for Comparisons between quantitative variables (Chan, 2003a), while for categorical data; Chi square (χ^2) test was

performed. Exact test was used instead when the expected frequency is less than 5 (Chan 2003b). P-values less than 0.05 were considered as statistically significant.

RESULTS

Table (1): socio-demographic characteristics of the studied groups

	Group 1 (Epilepsy group) N= 100	Group 2 (Control group) N= 100	P value
Age (year)			
Range	6-18	6-17	0.967
Mean \pm SD	10.45 \pm 3.16	10.40 \pm 2.75	
Gender			
Males	51 (51%)	48 (48%)	0.671
Females	49 (49%)	52 (52%)	
Father's occupation			
Self employed	72 (72%)	66 (66%)	0.018
Governmental job	19 (19%)	31 (31%)	
Died	6 (6%)	0 (0%)	
unemployed	3 (3%)	3 (3%)	
Mother's occupation			
Housewife	80 (80%)	76 (76%)	0.246
Self employed	16 (16%)	14 (14%)	
Governmental job	4 (4%)	10 (10%)	
Residency			
Urban	85 (85%)	100 (100%)	< 0.001
Rural	15 (15%)	0 (0%)	
Environmental risk factors			
Positive	25 (25%)	32 (32%)	0.273
Negative	75 (75%)	68 (68%)	

As shown in table (1), both epilepsy and control groups were matched for age, gender, mother's occupation and environmental risk

factors, otherwise they were statistically different concerning father's occupation and residency.

Table (2): comparison of neuropsychiatric disorders between epilepsy and control groups

		Group 1 (Epilepsy group) N= 100	Group 2 (Control group) N= 100	P value
Neuropsychiatric disorders	Yes			< 0.001
	Single	41 (41%)	28 (28%)	
	Multiple	24 (24%)	10 (10%)	
No		35 (35%)	62 (62%)	

Children with epilepsy were more likely to have neuropsychiatric disorders (65%) compared to healthy control children (38%), 24% of CWE had multiple neuropsychiatric disorders

compared to 10% in control group ($p= <0.001$) as shown in table (2). 89 % of CWE with neuropsychiatric comorbidities were newly diagnosed.

Figure (1): The frequency of individual neuropsychiatric disorders in epilepsy and control groups

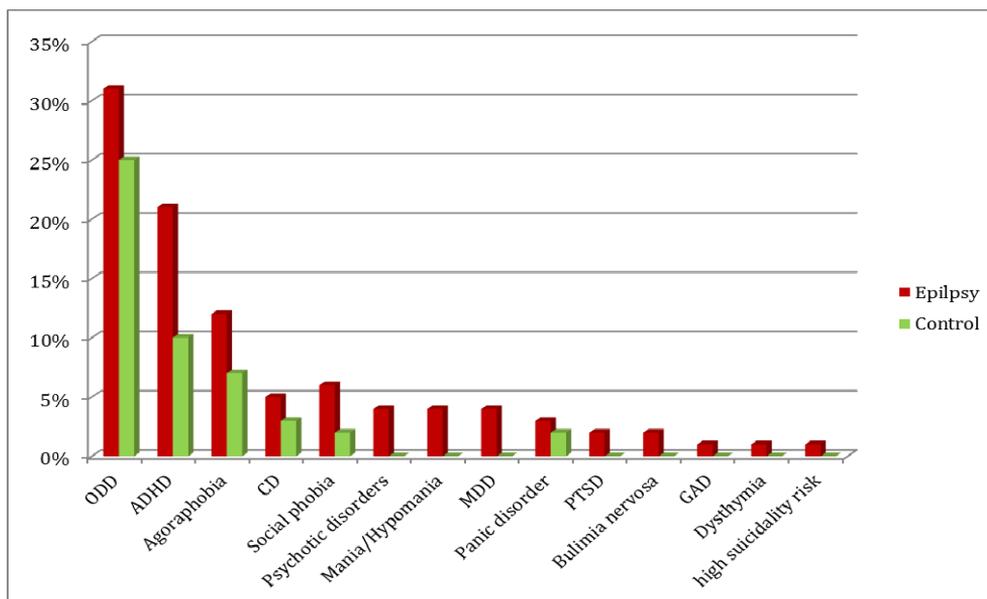


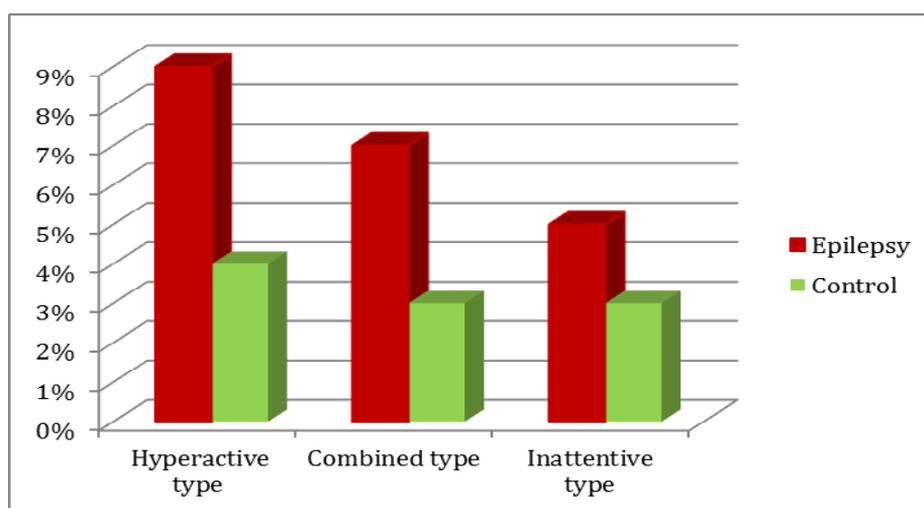
Figure (1) shows the frequency of each neuropsychiatric disorder in epilepsy and control groups, oppositional defiant disorder (ODD) was the most common in

epilepsy group (31%), followed by attention deficit hyperactivity disorder (ADHD) (21%), Agoraphobia (12%), conduct disorder (CD) (5%), social phobia

(6%), psychotic disorder (4%), mania/ hypomania (4%), major depressive disorder (MDD) (4%), panic disorder (3%), post-traumatic stress disorder (PTSD) (2%), bulimia nervosa (2%), generalized anxiety disorder (GAD) (1%), dysthymia (1%) and high suicidality risk (1%).

While in control group; only limited disorders were diagnosed within them, the most prevalent was ODD (25%) followed by ADHD (10%), Agoraphobia (7%), CD (3%), social phobia (2%) and panic disorder (2%).

Figure (2): Percentage of each ADHD subtypes in both epilepsy and control groups



For ADHD, figure (2) shows the percentage of each subtype in both epilepsy and control groups, where the hyperactivity type is the most predominant type in epilepsy group followed by combined type (9% and 7%) respectively, compared to control group (4% and 3%) respectively.

We also studied the relation between neuropsychiatric disorders and different risk factors in CWE including epilepsy related factors and socio-demographic factors (as demonstrated in table 3 and 4 respectively).

Table (3): Relation between neuropsychiatric disorders and epilepsy related factors in CWE

	Neuropsychiatric disorders		P value
	Yes N= 65	No N= 35	
Age of seizure onset (years) Range Mean \pm SD	0.00-16.00 5.16 \pm 4.01	0.58-14.00 6.65 \pm 3.49	0.043
Duration of Epilepsy (years) Range Mean \pm SD	0.02-17 5.42 \pm 3.90	0.16-10 3.49 \pm 2.68	0.017
Seizure type (onset of location) Focal Generalized Unknown	32 (49.2%) 29 (44.6%) 4 (6.2%)	7 (20%) 28 (80%) 0 (0%)	0.002
Epilepsy type Focal Generalized Combined generalized and focal Unknown	26 (40%) 22 (33.8%) 15 (23.1%) 2 (3.1%)	6 (17.14%) 25 (71.43%) 4 (11.43%) 0 (0%)	0.003
Seizure frequency during the past year Range Mean \pm SD	0.00-36 7.40 \pm 9.53	0.00-30 4.49 \pm 8.33	0.096
Time free from seizures < 1 month >or equal 1 day >or equal 1 month	10 (15.4%) 17 (26.1%) 38 (58.5%)	4 (11.4%) 9 (25.7%) 22 (62.9%)	0.914
Number of AEDs None Monotherapy Polytherapy	12 (18.5%) 44 (67.7%) 9 (13.8%)	6 (17.1%) 27 (77.1%) 2 (5.7%)	0.502
EEG characteristics Focal Generalized Focal to generalized Normal EEG	39 (67.2%) 12 (20.7%) 3 (5.2%) 4 (6.9%)	17 (56.7%) 5 (16.7%) 3 (9.9%) 5 (16.7%)	0.396

AEDs: anti-epileptic drugs, EEG: electroencephalography.

Concerning relation between neuropsychiatric disorders and epilepsy related factors, we found that the younger the age at seizure onset ($p=0.043$), the longer the duration of epilepsy ($p=0.017$), the focal seizure ($p=0.002$) and focal

epilepsy type ($p = 0.003$) the more the neuropsychiatric disorders among children with epilepsy, otherwise no other epilepsy related factors were significantly related, as shown in table (3).

Table (4): Relation between neuropsychiatric disorders and socio-demographic factors in CWE

	Neuropsychiatric disorders		P value
	Yes N= 65	No N= 35	
Age (years) Range Mean \pm SD	6-17 10.62 \pm 3.13	6-18 10.14 \pm 3.25	0.467
Gender Males Females	36 (55.4%) 29 (44.6%)	15 (42.9%) 20 (57.1%)	0.232
Father's occupation Self employed Governmental job Died unemployed	47 (72.3%) 9 (13.85%) 6 (9.23%) 3 (4.62%)	25 (71.4%) 10 (28.6%) 0 (0.0%) 0 (0.0%)	0.063
Mother's occupation Housewife Self employed Governmental job	52 (80%) 10 (15.4%) 3 (4.6%)	28 (80%) 6 (17.1%) 1 (2.9%)	1
Residency Urban Rural	57 (87.7%) 8 (12.3%)	28 (80%) 7 (20%)	0.304
Environmental risk factors Positive Negative	22 (33.8%) 43 (66.2%)	3 (8.6%) 32 (91.4%)	0.005

As regard socio-demographic factors, neuropsychiatric disorders were significantly related to environmental risk factors in CWE

($p= 0.005$), otherwise no other socio-demographic factors were significantly related, as shown in table (4).

DISCUSSION

Childhood epilepsy is associated with multiple comorbidities including social, emotional, cognitive and psychiatric impairment (**Bailey and Im-Bolter, 2018**). It is well known that all these comorbidities greatly affect the quality of life of both children and their families (**Bilgiç et al., 2018**).

Psychiatric disorders have long been studied in relation to epilepsy, however, prevalence rates show a wide variation from 21% to 60% depending on the population studied and differences in the method of study (**Alfstad et al., 2016**).

Several theories was suggested to explain this relationship between neuropsychiatric disorders and epilepsy; for example: considering that epilepsy is a systemic disorder and neuropsychiatric comorbidities is part of it (**Yuen et al., 2018**) and the bidirectional theory (**Kanner, 2017**) where presence of common neuronal network for both epilepsy and psychiatric disorder may explain this bidirectional relation (**Moshé et al., 2015**).

Berg and her colleagues criticize the bidirectional theory from three points; (1) most of studies that support this theory depend on parent-proxy

statements which biased by parental realization and reactions to the disease; (2) occurrence of periictal psychiatric symptoms complicate psychiatric and behavioral assessment; and (3) misdiagnosis of psychogenic non-epileptic seizures as epilepsy (**Berg et al., 2017**).

In our cross-sectional study we aimed to eliminate the biases from parent-proxy statements by directly examining the children using the MINI-KID interview (child version). We found that children with epilepsy were more likely to have neuropsychiatric disorders than children of healthy control group, similarly Li and his colleagues found that (41.4%) of children with epilepsy suffer from neuropsychiatric disorders as compared with the asthma group (15.7%) and the control group (10.0%) using the MINI-KID tool (**Li et al., 2018**), the lower prevalence in their study compared to our study may be explained by using parent version while we depend on the child version, also different population may have role in this difference.

Several studies was done to demonstrate the prevalence of neuropsychiatric disorders in children with epilepsy, one of them is a nationwide registry-based study in united kingdom aiming to describe the different

comorbidities with childhood epilepsy, they found that 43% of children with epilepsy suffer from psychiatric and developmental disorders (Aaberg et al., 2017).

Furthermore, all these studies recommend early screening for neuropsychiatric disorders in order to establish the early case finding and management, Reilly et al. found that 80% of CWE suffer from behavioral disorders and/or cognitive impairment, only one-third of them was previously diagnosed before their study (Reilly et al., 2014).

In our study, approximately 89% of CWE who suffer from neuropsychiatric disorder were newly diagnosed; this may be due to lack of awareness about psychiatric symptoms between parents, lack of screening and fear from stigma.

Concerning ADHD we found that ADHD was more prevalent (21%) among CWE compared to control group (10%) with the most predominant subtype was hyperactivity type, followed by combined type. Several studies approve the high prevalence of ADHD in CWE which may be explained by underlying brain dysfunction or frequent epileptiform discharge (Besag et al., 2016).

Choudhary and his colleagues found that 23% of children with epilepsy had ADHD with the most predominant subtype was the inattentive type (Choudhary et al., 2018). However, it is found that epilepsy related factors are not related to inattentive type of ADHD in children with average intelligence (Caplan, 2017).

Risk factors of neuropsychiatric disorders in children with epilepsy:

In contrast to the well-established fact that there is high prevalence of neuropsychiatric comorbidities in CWE, the etiology of this fact is not well established till now (Salpekar and Mula, 2018).

Several studies were conducted to study the relation between neuropsychiatric disorders and epilepsy variables including seizure frequency, age at seizure onset, duration of epilepsy, epilepsy types, and antiepileptic treatment, In our study we found that younger the age at seizure onset, more the duration of epilepsy, focal seizures at seizure onset and focal epilepsy the more the neuropsychiatric comorbidities, however it is not related to seizure frequency, number of AEDs and EEG characteristics.

Children with lower age at seizure onset (especially less than 3 years old) or those with long duration of epilepsy were more liable to develop neuropsychiatric disorders and these findings were consistent with other studies (Alfstad et al., 2016; Li et al., 2018). Early childhood epilepsy dramatically affects brain development with high risk for other developmental brain disorders including psychiatric and behavioral disorders (Berg et al., 2017).

Concerning relation between focal epilepsy and neuropsychiatric disorders, our results are in line with Thome-souza et al. study (Thome-souza et al., 2004), furthermore, many studies approve that certain neuropsychiatric disorders were more common with certain types of focal epilepsy; for example the relation between temporal lobe epilepsy and psychiatric disorders specially schizophrenia (Nakahara et al., 2018) and the relation between frontal lobe epilepsy and cognitive function (Verche et al., 2018).

In our study we found that neuropsychiatric disorders were not related to seizure frequency, time free from seizures and number of AEDs. These findings were consistent with Alfstad et al. findings (Alfstad et al., 2016).

We interpret these results to several factors including that children with polytherapy representing only 11% from our sample and most parents had no accurate document for number of seizures during the past year and time free from last seizure.

Also there was no relation between EEG characteristics and neuropsychiatric disorders in CWE, the same result was found in several studies (Alfstad et al., 2016; Li et al., 2018; Oguz et al., 2002; ott et al., 2001), however further studies for relation between individual neuropsychiatric disorders and EEG characteristics is recommended.

We also study the relation of neuropsychiatric disorders with socio-demographic and environmental risk factors in CWE, and we found that environmental risk factors are significantly related to of neuropsychiatric disorders.

It is important to include both epilepsy-related and psychosocial factors in an integrated model to understand the complex relationship between epilepsy and psychiatric disorders (Austin and caplan, 2007).

The interaction within the immediate social circle around the children (e.g., parents, teachers,

peers) greatly influence their development and it is found that these interactions tend to be less positive for CWE compared to their peers (Bailey and Im-Bolter, 2018).

Several researches study the etiology of high prevalence of psychiatric disorders in CWE, but most of them tend to explain it by biological factors while few studies look for the social factors, Labudda et al. found that emotional and sexual childhood maltreatment experiences is a general risk factor for psychiatric comorbidities in patients with epilepsy (Labudda et al., 2017).

Thornton et al. found that there were positive correlation between family function and emotional/behavioral disorders in CWE compared to their non-epileptic siblings; they conclude that there is favorable outcome for most CWE and their non-epileptic siblings in families with strong function, while the opposite condition was found in families with weak function. In families with average function, CWE had a higher prevalence of problems than their non-epileptic siblings (Thornton et al., 2008).

CONCLUSION

Our study demonstrated that neuropsychiatric disorders are

more common in children with epilepsy. Approximately 89% of them were not diagnosed. These findings ensure the insistent need for screening programs for children with epilepsy and health education of their parents about psychiatric symptoms. We also found that a younger age at seizure onset, long duration of epilepsy, focal epilepsy and presence of environmental risk factors was all significantly related to neuropsychiatric comorbidities in children with epilepsy.

Our study emphasizes the importance of direct interview with children in order to avoid under diagnosis of many neuropsychiatric disorders

LIMITATIONS

The basic limitation of our study is that most parents didn't document the seizure frequency for their children, especially for children with uncontrolled seizures, so we interpret the result concerning association between seizure frequency and neuropsychiatric disorders with caution.

RECOMMENDATIONS

We recommend regular screening of children with epilepsy for neuropsychiatric comorbidities, health education programs for parents about the

nature of the epilepsy disease and its comorbidities and multicenter study on a large sample for good understanding to the multiple variables associated with neuropsychiatric comorbidities in children with epilepsy.

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تقييم الاضطرابات النفسية والعصبية المصاحبة للأطفال المصريين المصابين بالصرع باستخدام المقياس العالمي المصغر للفحص النفسي العصبي للأطفال (ميني كيد)

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القاهرة - مصر

أساسيات:

يعتبر الصرع واحدًا من أكثر الأمراض العصبية شيوعًا بين الأطفال، مع ارتفاع معدل الإصابة بأمراض مصاحبة متعددة.

الهدف:

الهدف من هذه الدراسة هو تحديد معدل الأمراض النفسية والعصبية المصاحبة للأطفال المصابين بالصرع وتحليل العلاقة بينها وبين العديد من عوامل الخطر.

الطرق والأشخاص:

من خلال استخدام المقياس العالمي المصغر للفحص النفسي العصبي للأطفال (ميني كيد) (نسخة الطفل)، تم تقييم مائة طفل مصاب بالصرع ومائة آخرين من الأطفال الأصحاء، وذلك بالعيادة الخارجية ووحدة الأمراض العصبية بقسم طب الأطفال في مستشفى الزهراء الجامعي. بالإضافة لذلك؛ تم استخدام مقياس فندربيلت لفرط الحركة ونقص الانتباه (نسخة الآباء) لتأكيد تشخيص اضطراب فرط الحركة ونقص الانتباه، كذا تم جمع البيانات الاجتماعية والديموغرافية والسرييرية من خلال أخذ تاريخ مفصل من الوالدين.

النتائج:

الأطفال المصابون بالصرع يعانون من الاضطرابات النفسية والعصبية بنسبة أعلى وبدرجة ملحوظة (65 %) مقارنة بالأطفال الأصحاء (38 %)، كذا يعاني 24% من الأطفال المصابين بالصرع من اضطرابات نفسية وعصبية متعددة مقارنة مع 10 % من المجموعة الضابطة .

يزداد احتمال الإصابة بالاضطرابات النفسية والعصبية بين الأطفال المصابين بالصرع كلما كان الطفل أصغر سنًا عند أول نوبة للصرع، وكلما طالت الفترة الزمنية لمرض الصرع، كذا مع النوبات من النوع البؤري والصرع البؤري ووجود عوامل خطر بيئية .

الاستنتاج :

الاضطرابات النفسية والعصبية أكثر شيوعا بين الأطفال المصابين بالصرع لذا ننصح بضرورة التحري عن الأمراض النفسية والعصبية عندهم بشكل دوري، وعمل برامج للتثقيف الصحي للأباء حول طبيعة مرض الصرع والأمراض المصاحبة له.