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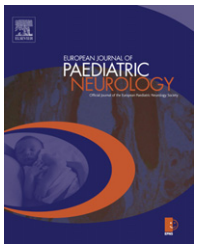

Original article

Seizures and intellectual outcome: Clinico-radiological study of 30 Egyptian cases of tuberous sclerosis complex

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ABSTRACT

Background and objectives: Tuberous sclerosis complex (TSC) is a multi-systemic disorder that involves primarily CNS, skin, kidney and heart. The aim of this study is to determine whether seizures type, interictal EEGs and tubers burden in MRI are correlated to seizure and intellectual outcome, and to identify the clinical risk factors for mental retardation and developing autism in these patients.

Methods: This was a prospective study that was conducted on 30 Egyptian children with tuberous sclerosis complex (TSC), diagnosed according to the criteria of National Institutes of Health consensus conference revised the diagnostic criteria for TSC. All patients underwent clinical and psychometric evaluation, interictal EEG, and MRI brain.

Results and conclusions: We found that poor intellectual outcome is related to early onset of seizures, infantile spasms, severely epileptogenic EEG findings and tuber burden on the Left side. Autistic behavior is related to seizure type (more with infantile spasms), severely epileptogenic EEG findings, frontal location of tubers and higher number of tubers (>8).

1. Introduction

Tuberous sclerosis complex (TSC) is a multi-systemic disorder that involves primarily central nervous system, skin, kidney and heart. It presents with extremely variable clinical manifestations[1] and the classic clinical triad of mental retardation, epilepsy and adenoma sebaceum is reported in only one-third of the cases.[2,3]

The neurological manifestations of TSC are particularly challenging and include infantile spasms,[4] which are the most common seizure type in the first year of life, and these are sometimes preceded or followed by partial seizures.[5] A wide spectrum of cognitive, behavioral and psychiatric problems are frequently encountered, especially in those with earlier onset epilepsy.[4,6]

Two genes, TSC1 and TSC2 have been identified,[7] the TSC1 gene mapping to 9q34 encodes a protein named hamartin[8]; whereas, the TSC2 gene mapping to chromosome 16p13.3 encodes a protein named tuberin.[9] TSC genes act as tumor suppressors,[10] their mutation leads to hamartomatous lesions in various organs. These genes encode proteins that modulate cell function via the mammalian target of rapamycin complex 1 (mTOR-1) signaling cascade and serve as keystones in regulating cell growth and proliferation.[4] Antagonism of the

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mTOR pathway with rapamycin may provide new therapeutic options for TSC patients.[4,11]

The characteristic brain lesions in TSC are cortical tubers, subependymal nodules, and giant cell tumors; cortical tubers are the lesions which are directly linked to epileptogenesis, and numerous MRI studies showed some correlations between presence or severity of epilepsy and number, size and location of tubers.[12]

The aim of this study is to determine whether seizure type at onset, interictal electroencephalograms (EEGs) and tubers burden as seen with magnetic resonance imaging (MRI) are correlated to seizure and intellectual outcome. Further, to identify the clinical risk factors for mental retardation and developing autism in these patients.

2. Methodology

2.1. Study design and participant characteristics

This was an observational, prospective study that was conducted on 30 Egyptian children with TSC, with age ranged from 1.3 to 8.9 years. The diagnosis of TSC was established according to the criteria of National Institutes of Health consensus conference revised the diagnostic criteria for TSC,[13] and this was based on presence of brain MRI finding of cortical tubers and/or subependymal nodules associated with dermatological findings of TSC (2 major criteria). Eligibility criteria: patients were eligible in the current study when they had (1) definite diagnosis of Tuberous Sclerosis; (2) seizures during the first year of life; (3) coherence of follow-up visits for at least 6 months.

2.2. Patient recruitment and evaluation

Patients were recruited from the Neuropediatrics clinic of Fayoum University Hospitals and from Neurology Outpatient Department of Cairo University Hospitals. Prior to the study commencement, parents of all patients gave a written informed consent approved by Neurology Department Review Boards in Cairo University.

2.2.1. Medical evaluation

All patients were thoroughly evaluated by general and neurological examinations. A detailed developmental history was taken and history of seizures onset and semiology was analyzed by eye-witness parents. During the follow-up period, ECHO and abdominal ultrasound were requested for all included children.

2.2.2. Psychological assessment and psychometric tests

Estimates of the children's capabilities were made using the following standardized cognitive tests/appropriate for age (1) The mean developmental index (MDI) of Bayley scales of infant development-second edition[14] (BSID-II) for children $\leq$3 years; (2) Wechsler Preschool and Primary Scale of Intelligence-Revised[15] (WPPSI-R) "for children age from >3 to 7 years", and (3) Wechsler Intelligence Scale for Children-III[16] (WISC) "for those >7 years". Mental retardation was diagnosed if intelligence quotient (IQ) was below 70.

A clinical interview with parents was done by psychiatrist (M.N) to screen for autism spectrum disorders (ASD) or Attention deficit hyperkinetic disorders (ADHD). The interviewer was not blinded to seizure history as this often arose spontaneously during the interview. Children with a possible ASD were assessed using the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule-Generic (ADOS-G),[17] while those with possible ADHD were subjected to Vanderbilt Assessment Scale – Parent Informant (VAS-P).[18] Thereafter, diagnoses were assigned according to Diagnostic and Statistical Manual of Mental Disorders. 4th edition-Text Revision (DSM IV-TR).[19] Children with autism, Asperger's syndrome or pervasive developmental disorder not otherwise specified (PDD/NOS) were deemed to have ASD; those with ADHD were categorized into predominantly inattentive, predominantly hyperactive–impulsive, or combined subtype.

2.2.3. Interictal digital EEG records

EEGs were recorded to all included patients for at least 30 min using a 32-channel NIHON KOHDEN – Neurofax, EEG–9000 Ver. 05-71 (EEG-9200k, CE), based on the international 10–20 system of electrode placement. All EEGs were carried out either under standard conditions or after sedative premedications (chloral hydrate) in non-cooperative children. Hyperventilation for 3 min was used whenever possible and intermittent photic stimulation was used for all patients. The EEG records were interpreted based on visual analysis by two of the authors (H.A and H.S) in the same setting according to definitions of the International Federation of Clinical Neurophysiology.[20] EEG traces were classified into; (1) normal record, (2) mildly epileptogenic abnormalities (focal spikes, sharp slow, or spike slow), or (3) severely epileptogenic abnormalities that included multifocal discharges, typical or modified hypsarrhythmia, or suppression burst.

2.2.4. Treatment options

Conjoint therapeutic decisions were made for all included patients using the same therapeutic protocol according to the NICE guidelines.[21] Response to drug therapy was assessed in patients with a minimum follow up of 6 months and graded by noting the reduction in seizures frequency and caregiver satisfaction. Accordingly; patients were categorized into 5 groups; (1) seizures freedom ($n = 5$), (2) seizure reduction $\geq$ 90% as compared to the baseline ($n = 4$), (3) partial response with satisfactory adaptation of the caregivers with seizures reduction > 50% and <90% ($n = 2$), (4) partial response with unsatisfactory adaptation of caregivers with seizures reduction <50% ($n = 14$), (5) no response when there was no change in the number of seizures with adequate therapy ($n = 5$). Patients in groups 1, 2 and 3 were considered to have favorable seizure outcome ($n = 11$); patients in groups 4 and 5 were considered to have poor seizure outcome ($n = 19$).

2.2.5. Brain imaging

All patients were submitted to Brain Magnetic resonance imaging (MRI) on a 1.5 T Phillips Intera ® scanner. The image protocol included: axial T1, T2 and FLAIR (at 5 mm slices thickness), sagittal T1 WI (at 5 mm slices thickness), and coronal T2 WI (at 3 mm slices thickness). For contrast

Table 1 – Clinical and EEG data in study groups.

Parameters		Favorable seizure outcome ($n = 11$)	Poor seizure outcome ($n = 19$)	P-value
		Number (%)	Number (%)	
Gender	Males	6 (54.5%)	10 (52.6%)	0.77
	Females	5 (45.5%)	9 (47.4%)	
Age at seizure onset	< 6 mo	1 (9.1%)	15 (79%)	0.001*
	≥ 6 mo	10 (90.9%)	4 (21%)	
Seizure type	IS	2 (18.2%)	15 (79%)	0.03*
	PS	3 (27.3%)	2 (10.5%)	
	PS + SG	6 (54.5%)	2 (10.5%)	
Consanguinity	Positive	0 (0%)	4 (21%)	0.71
	Negative	11 (100%)	15 (79%)	
Interictal EEG	Severe epileptic discharges	2 (18.2%)	15 (79%)	0.03*
	Mild epileptic discharges	2 (18.2%)	2 (10.5%)	
	Normal	7 (63.6%)	2 (10.5%)	

IS: infantile spasms, PS: partial seizures, SG: secondary generalization.

enhancement; intravenous administration of gadolinium (0.1 mmol/kg) was done. Images were interpreted regarding the presence of cortical tubers and subependymal nodules. Both were classified according to their number and size; cortical tubers were further classified according to their location. The size of cortical tubers and nodules was classified into; large (if >30 mm), medium (if 10–30 mm), and small (if <10 mm).

2.3. *Data analysis*

Data management was performed using the Statistical Package for Social Sciences (version 15.0; SPSS Inc., Chicago, IL, USA). Compute standard descriptive statistics (e.g., mean, standard deviation) is used to summarize the data. Nominal data were analyzed using simple X2 test, while independent-sample T-test procedure was used to compare means for two groups of cases; for more than two groups, data were evaluated with one-way analysis of variance (ANOVA). A probability value (P value) less than 0.05 was considered significant.

3. Results

3.1. *Clinical data*

The current study included 30 Egyptian patients with definite TSC and epilepsy; their age range was from 1.3 to 8.9 years (mean ± SD: 4.66 ± 2.29) and male to female ratio was (1.14:1). All enrolled children had had characteristic dermatological findings as inclusionary criteria. Negative consanguinity with absence of family history was detected in 86.7% of cases; no case in the current study had cardiac manifestations or renal

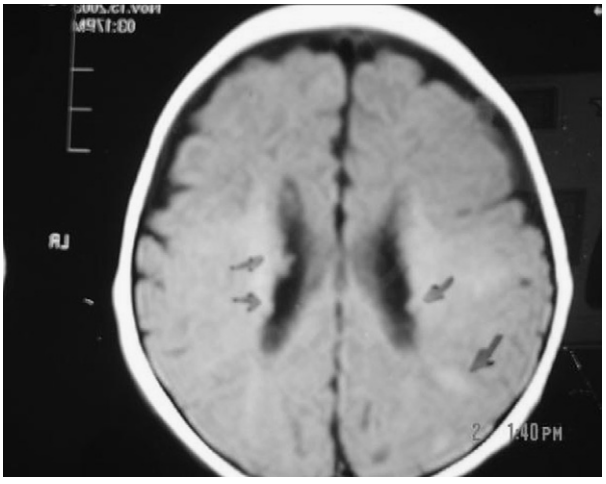

Fig. 1 – Axial Flair image for 2 years old boy showed multiple subependymal nodules and 2 cortical tubers in left parietal lobe, he was manifested by infantile spasms and normal mental development (favorable outcome).

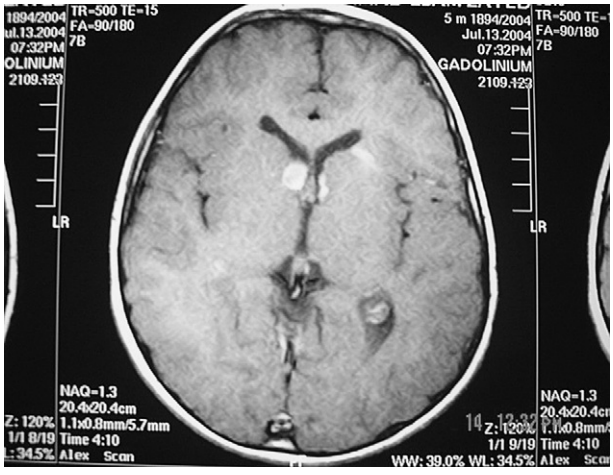

Fig. 2 – Axial T1 weighted image for 3.6 years old girls showed medium sized subependymal nodule (10–30 mm) with partial seizures and autistic features (poor seizures outcome).

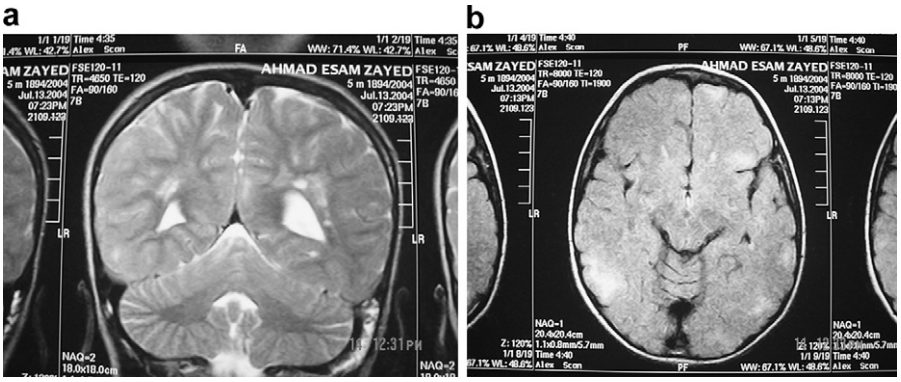

Fig. 3 – Coronal T2 weighted image (a), and axial Flair (b) showed high signal intensity of cortical tubers in temporal lobes in 2-year male patient with infantile spasms.

problems by clinical evaluation, ECHO heart and abdominal ultrasonography.

All evaluated children were divided into two seizure outcome groups; (1) Group I (favorable seizure outcome) ($n = 11$), and (2) Group II (poor seizure outcome) ($n = 19$). The mean age was 4.9 ± 2.4 years in children with favorable seizure outcome (group I) and it was 4.3 ± 2.1 years in those with poor seizure outcome (group II). The age of onset of seizures ranged from 3.3 to 31 months with mean age of onset was 11.9 ± 5.5 months in group (I), and 5.3 ± 3.7 months in group (II). Infantile spasms were present in 17 cases (56.7%) and partial seizures in 13 cases (43.3%) either simple or complex with or without secondary generalization.

3.2. *EEG results*

EEG showed picture of Hypsarrhythmia "typical or modified" and/or Suppression burst pattern in 17 cases (severe epileptic discharges); while, focal epileptic discharges were recorded in only 4 cases (Table 1).

Table 2 – MRI findings in study groups.

MRI findings		Favorable seizure outcome ($n = 11$)	Poor seizure outcome ($n = 19$)	P-value
Cortical tubers		Number (%)	Number (%)	
Number	1–4	5 (45.5%)	2 (10.5%)	0.02*
	5–8	4 (36.3%)	5 (26.3%)	
	> 8	2 (18.2%)	12 (63.2%)	
Size	Small	10 (90.9%)	16 (84.2%)	0.69
	Medium	1 (9.1%)	2 (10.5%)	
	Large	0 (0%)	1 (5.3%)	
Location	Frontal	2 (18.2%)	10 (52.6%)	0.09
	Temporal	2 (18.2%)	4 (21%)	
	Parietal	7 (63.6%)	4 (21%)	
	Occipital	0 (0%)	1 (5.3%)	
Subependymal nodules				
Number	1–4	7 (63.6%)	3 (15.8%)	0.01*
	5–8	3 (27.3%)	3 (15.8%)	
	> 8	1 (9.1%)	13 (68.4%)	
Size	Small	11 (100%)	17 (89.5%)	0.000*
	Medium	0 (0%)	2 (10.5%)	
	Large	0 (0%)	0 (0%)	

3.3. *Radiological analysis*

MRI findings included cortical tubers and subependymal nodules (Figs. 1–3). Most of our cases had small-sized cortical tubers and nodules (<10 mm). Regarding tubers location; 52.6% of cases with poor seizure outcome had their tubers in frontal lobe and 63.6% of cases with favorable seizure outcome in parietal lobe (Table 2).

3.4. *Intellectual and behavioral outcome*

Mental subnormalities were detected in 19 children (63.3%); and it was more encountered in patients with poor seizure outcome ($P = 0.01$). Behavioral disorders were detected in 16 children (53.3%), most of them (12/16; 75%) had ASD (8 had typical autism, 3 had high functioning autism "HFA" and one child had PDD/NOS); other 4 patients (25%) had ADHD-hyperactive–impulsive type (Table 3).

Mental subnormalities were associated with earlier seizure onset, infantile spasms as presenting epileptic semiologies, encephalopathic EEG pattern and left sided hemispheric tubers burden. Moreover; 52.2% of cases with subnormal mentality had their cortical tubers mainly in frontal lobe while 63.6% with normal mentality had the tubers in parietal lobe mainly (Table 4). Autistic behavior was associated also with infantile spasms as presenting epileptic manifestations, encephalopathic EEG pattern, higher numbers of cortical tubers and their frontal location (Table 5).

4. Discussion

Tuberous sclerosis complex (TSC) is a congenital syndrome with autosomal dominant inheritance and variable phenotypic expression that was documented in 20% of cases[2]; while, about 80% of affected patients have a new mutation.[22] In the current study, genetic analysis were not included; however, negative consanguinity with absence of family history was

Table 3 – Intellectual and behavioral outcome in study groups.

Intellectual outcome		Favorable seizure outcome ($n = 11$)	Poor seizure outcome ($n = 19$)	P-value
		Number (%)	Number (%)	
Mentality	Severe MR	0 (0%)	5 (26.3%)	0.01*
	Moderate MR	1 (9.1%)	10 (52.6%)	
	Mild MR	1 (9.1%)	2 (10.5%)	
	Normal mentality	9 (81.8%)	2 (10.5%)	
Behavior	Autistic	2 (18.2%)	10 (52.6%)	0.38
	Hyperkinetic	1 (9.1%)	3 (15.8%)	
	Normal	8 (72.7%)	6 (31.6%)	

detected in majority of cases (86.7%) that might suggest new mutations rather than dominant inheritance.

The most common neurological manifestations of TSC are epilepsy, mental retardation, and autistic behavior.[22,23] Epilepsy occurs in up to 90% of patients and it is often incapacitating, with a poor response to anticonvulsant medications.[22] In the current study, 63.3% (19/30) of our cases had poor seizures outcome; most of them were with subnormal mentality, while 36.7% (11/30) had favorable seizure outcome and most of them were of normal mentality. The presenting seizure semiology was infantile spasms (IS) in 56.7%, and partial seizures in 43.3% of our cases. In a recent retrospective chart review, Chu-Shore et al.[24] found that 37.8% had a history of infantile spasms and 54.1% had developed multiple seizure types, not including IS; however, higher percentage of IS in our study could be attributed to age specification as we included a younger age group (the mean ± SD in our series was: 4.66 ± 2.29 years), and IS is a catastrophic form of epilepsy found only in infants and young toddlers, with the peak incidence between 4 and 7 months of age.[25]

Hymann and Whittemore[13] observed that the younger the age of onset of clinical manifestations, the greater the likelihood of mental retardation; a fact that was documented in the current study and was also previously emphasized by Curatolo[26] and Dulac et al.[27] Moreover; in the current study, 73.7% of patients with mental subnormality (IQ <70) had infantile spasms, and 78.9% of them had severe EEG abnormalities. This is in agreement with Suzanne et al[6] who reported mental subnormality (IQ <70) in 64% of TSC patients with infantile spasms.

Regardless the complexity of clinical manifestations of this disorder; cognitive deficits and behavioral problems remain the area of greatest concern to caregivers; hence, this spectrum should be targeted during interventional approaches.[28] Even in patients with normal intellectual abilities, there is higher risk for specific neuropsychologic deficits that would suggest a consistent fronto-striatal circuits dysfunction by TSC – related neuropathology leading to abnormalities in regulatory behaviors and executive working memory.[29]

In the current study; 52.6% of cases with subnormal mentality had their tubers in frontal lobe and the same location for the most cases (75%) of autistic behavior; however, an evidence of temporal lobes involvement in early-onset refractory epilepsy, functional deficits and autism was clarified by Curatolo et al.[30] and Bolton et al.[31] Nevertheless; the presence of tubers in the temporal lobes appeared to be a necessary but not sufficient risk factor for the development of an autism spectrum disorder.

The incidence of autism in TSC may be significantly higher than cardiac and renal abnormalities.[30] In the current study, 12/30 (40%) of our patients had autistic behavior. Owing to these findings, we propose a routine screening of autistic behavior in patients with TSC.

Cortical tubers and subependymal nodules are the principal neuropathological hallmark of TSC. According to Crino et al.,[23] there is a significant relation between the number of cortical

Table 4 – Comparison of both groups of normal and subnormal mentality according to different parameters.

Parameters			Normal mentality ($n = 11$)	Mental subnormality ($n = 19$)	P-value
			Number (%)	Number (%)	
Age at seizure onset	< 6 months		2 (18.2%)	14 (73.7%)	0.02*
	≥ 6 months		9 (81.8%)	5 (26.3%)	
Seizure type	Infantile spasms		4 (36.3%)	14 (73.7%)	0.04*
	Other seizure types		7 (63.6%)	5 (26.3%)	
EEG	Encephalopathic/severe abnormalities		4 (36.3%)	15 (78.9%)	0.05
	Other findings/normal		7 (63.6%)	4 (21%)	
MRI findings	Tubers location	Frontal	2 (18.2%)	10 (52.6%)	0.09
		Temporal	2 (18.2%)	4 (21%)	
		Parietal	7 (63.6%)	5 (26.3%)	
	Tubers number	> 8	2 (18.2%)	11 (57.9%)	0.07
		≤ 8	9 (81.8%)	8 (42.1%)	
	Hemispheric tubers burden	Mainly left sided	4 (36.3%)	17 (89.5%)	0.02*
		Right sided/bilateral	7 (63.6%)	2 (10.5%)	

Table 5 – Comparison between the two groups of normal and autistic behavior according to different parameters.

Parameters			Normal behavior ($n = 14$)	Autistic behavior ($n = 12$)	P-value
			Number (%)	Number (%)	
Age at seizure onset	< 6 months		6 (42.9%)	8 (66.7%)	0.25
	≥ 6 months		8 (57.1%)	4 (33.3%)	
Seizure type	Infantile spasms		5 (35.7%)	11 (91.7%)	0.01*
	Other seizure types		9 (64.3%)	1 (8.3%)	
EEG	Encephalopathic/severe abnormalities		4 (28.6%)	10 (83.3%)	0.01*
	Other findings/normal		10 (71.4%)	2 (16.7%)	
MRI findings	Tubers location	Frontal	3 (21.4%)	9 (75%)	0.04*
		Temporal	3 (21.4%)	3 (25%)	
		Parietal	8 (57.1%)	0 (0%)	
	Tubers number	> 8	1 (7.1%)	11 (91.7%)	0.001*
		≤ 8	13 (92.9%)	1 (8.3%)	

tubers and IQ and also they documented that the greater the number of tubers, the more neurologically impaired is the patient; this observation was also documented by Bolton et al.[31] These reports go in accordance with our results.

Zaroff et al.[32] reported that bilateral cortical tubers and early age of seizure onset were significantly related to impaired cognitive functioning. On the other hand; the tuber/brain proportion (TBP) was recently emphasized by Jansen et al.[33] as a better determinant of seizures and cognitive function than the number of tubers. They defined TBP as a proportion of the total brain volume occupied by tubers that is characterized on 3Ds fluid-attenuated inversion recovery MRI with an automated tuber segmentation program. They found that TBP was inversely related to the age at seizure onset and to the intelligence equivalent.

In conclusions, earlier age of seizures commencement (<6 months) is associated with poor seizure outcome and poor intellectual capabilities. Infantile spasms and severely epileptogenic EEG patterns are related to the poor seizure outcome, poor intellectual capabilities and autistic behavior. Higher tubers numbers is associated with poor seizure outcome and autistic behavior. Left sided tuber burden is associated with poor intellect, while frontal location is more encountered in ASD. So, close follow up for the mental development and early control of seizures are recommended in a trial to reduce the risk factors of poor outcome. Also early diagnosis of autism will allow for earlier treatment and the potential for better outcome for children with TSC.

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