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Refractory epilepsy in preschool children with tuberous sclerosis complex: Early surgical treatment and outcome

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ABSTRACT

Purpose: Epilepsy surgery has been shown to be effective in treating focal epilepsy related to tuberous sclerosis complex (TSC). We analyzed the advantage of early surgical management in terms of seizure frequency and development.

Method: We retrospectively studied the 15 patients younger than 6 years who underwent resective surgery between 2006 and 2016. Fourteen of them had invasive monitoring while the 15th was operated on under corticography.

Results: Epilepsy began before 5 months of age in all patients. Overall 13 patients (86%) had a dramatic improvement of epilepsy after surgery (Engel 1 and 2) including 9 patients (60%) seizure free (Engel 1 A). In the group of 9 patients younger than 20 months at the time of surgery who presented with catastrophic epilepsies, 77% are Engel 1 A and the other 23% Engel 2. In this subpopulation, no one developed autism and four (44%) regained normal development.

Conclusions: In early onset epilepsies associated with TSC, surgical treatment is highly effective, in particular when performed early. Invasive monitoring contributes to the successful outcome. Those data have to be confirmed by multicentric studies including quantitative analyses of the recordings.

1. Introduction

Tuberous sclerosis complex (TSC) is a multisystem disorder with autosomal dominant inheritance and a high rate of de novo pathogenic variants (60%).The incidence of this illness is 1/7000–8000 people. Diagnostic criteria for TSC were first defined by Roach and Gomez [1] and recently reviewed by Northrup [2].

Neurological symptoms are common in TSC as epilepsy occurs in 80–90%, cognitive impairment in 50% and autism spectrum disorders (ASD) in up to 40%. Neurological symptoms are attributable to the neuroanatomic abnormalities (cortical tuber, white matter abnormalities, subependymal nodules and subependymal giant cell tumors); furthermore, the elements of neuropsychiatric disorders in TSC may be directly attributable to dysregulation of mTOR signalling [3]. Cortical tubers are the lesions underlying epilepsy, and the epileptogenicity is located either within the tuber [4,5], at the periphery [6] or both [7].

Of the individuals with TSC who develop epilepsy, almost 2/3 have seizure onset in the first year of life. One third of them will develop infantile spasms and 60% of them have drug refractory epilepsy [8]. The presence of refractory epilepsy and infantile spasms in TSC has been shown to be significantly associated with cognitive impairment, ASD and psychiatric disorders [9–11,3]. Moreover, any type of poorly controlled seizures is an important predictor of ASD and, epilepsy, when refractory, plays an aggravating role in the so-called Tuberous sclerosis associated neuropsychiatric disorders (TAND) [3].

Epilepsy surgery has been shown to be effective in some patients with drug-resistant epilepsies in several retrospective series [12–17] with a cessation of the seizures in up to 50–60% ; epilepsy surgery required a careful selection of the patients based upon imaging and electrophysiological data including scalp and, if needed, invasive EEG-recordings in order to accurately identify the epileptogenic zones(s) before removal.

A good outcome after surgery has been shown to be associated with an improvement of quality of life and neurodevelopmental disorders. In order to support the evidence of the benefits of an early childhood surgery on epilepsy and neurodevelopmental-associated disorders, we are reporting on a single-centre experience of preschool children operated on for epilepsy while emphasizing the selection criteria, the surgical procedures and the outcome focusing on seizure outcome using Engel classification [18] and on cognitive and ASD features outcomes.

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Table 1
Demographic data.

Patient number	Sex	Age at Sz onset (weeks)	Infantile spasms	genetic	presurgical neurological exam	Tuber number on MRI	calcified tuber	calcificated tuber topography	calcificated tuber/ EEG focus correlation	Age at surgery (Months)	type of surgery	side of surgery	post surgical exam (months)	Follow up duration (years)	Engel	number of AED at the last visit
1	F	3 (IS)	yes	TSC2 (de novo)	L hemianopia and hemiparesis	2	1	L parietal	yes	8	Parieto-occipital disconnection + resection	R	R handed stable	5.9	1	2
2	M	16	Yes (2 Mo)	TSC2 (de novo)	R handed, no deficit; mentally delayed	4	1	L frontal	yes	33	anterior frontal resection	L	stable	7	4	4
3	F	29	no	TSC1 (de novo)	normal, L handed	1	0			40	opercular and anterior parietal	L	permanent R hemiparesis	6.4	1	0
4	F	6 (IS)	yes	TSC2 (inherited)	L handed, good visual contact and interactions	2	1	L mesial parieto-occipital	yes	13	mesial parietal resection	L	L handed R inf quadranopia	7.2	1	2
5	M	0,2	no	NA (inherited)	bilateral gripping, good visual contact and interaction L hemianopia	3	1	R temporo-parieto-occipital	yes	8	temporal resection including mesial structures + PO disconnection	R	R handed (stable)	6.2	2	1
6	F	0,2	no	TSC2 (de novo)	good visual contact and interactions R mild hemiparesis, beginning of voluntary gripping	2	1	L frontal	yes	5	frontal resection and disconnection sparing motor strip + opercular resection	L	mild hemiparesis agravation	6.5	1	0
7	F	24	yes	NA (de novo)	good visual contact and interactions; L hand gripping slight right hemiparesis	3	1	L parietal	yes	8	centro-parietal	L	stable	5.4	2	2
8	M	18	no	TSC2 (inherited)	head holding visual contact smiling R hemianopia no gripping	2	1 (small)	L occipital	yes	7	occipital and neigboring temporo-parietal areas resection	L	L handed stable	4.7	1	1
9	M	2	Yes (8 Mo)	TSC2 (inherited)	R handed (L hemiparesis)	1	1 (small)	R insular	yes	43	operculo-insular resection	R	L hemiparesis	4.3	3	3
10	F	0,2	yes (4 Mo)	TSC2 (inherited)	R hemianopia, R hand neglect, L hand gripping	4	1 (small)	L parietal	yes	16	parieto-occipital resection	L	improvement of L hand utilisation	4.5	1	1
11	M	9 (IS)	yes	négative (inherited)	R handed (slight L hemiparesis)	4	1	R frontal	yes	54	fronto-insular resection	R	L hemiparesis improved	3.4	1	1 and VNS
12	M	55 (IS)	yes	TSC1 (inherited)	L hemianopia	1	1	R occipital	yes	19	occipital and temporo-occipital jonction resection	R	stable R handed	2.8	1	0
13	F	3	no	TSC2 (de novo)	L handed (preoperative R hemiparesis)	2	1	L central	yes	45	central resection	L	transcient leg deficit aggravation	2.1	2	3
14	F	34 (IS)	yes	NA (de novo)	no neurological deficit, L handed	1	1	L frontobasal	yes	66	anterior frontal and orbitofrontal resection	L	no change	1.,9	2	2
15	F	3	no	TSC2 (de novo)	L hemiparesis	1	1	Left Central	yes	7	central resection	R	slight hemiparesis aggravation, no L hand gripping	2.3	1	0

IS: Infantile spasms; L: left; R: Right; NA: not available; Sz: Seizure; MO: Months; VNS: Vagus nerve stimulation.