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MOTOR CHANGES, EXTENT OF THE LESION AND SEVERETY OF EPILEPSY IN THE ULEGERIA/ PORENCEPHALIC CYST SPECTRUM IN YOUNG ADULTS

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Abstract: We evaluated the relation between porencephaly cysts (PC) and/or ulegyria (U) with epilepsy and activities of daily living (ADLs) in patients with hypoxic-ischemic encephalopathy (HIE). Twenty one HIE patients were evaluated; lesion was verified using magnetic resonance images (MRI), the epileptic status using electroencephalogram (EEG) analysis and ADLs using functional scales. MRI analysis revealed U in 15 patients (71%), PC in 2 patients (9.8%) and combined U and PC brain lesions in 4 patients (19.2%). We found no association between location, extension and severity of U/PC with epilepsy. Both lesions were associated to motor impairment.
Combination of U/PC is more debilitating and should be focus of more intensive rehabilitation procedures.
Keywords: Epilepsy, Ulegyria; Hypoxic-ischemic encephalopathy, Motor function

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is an important cause of neurological deficits in humans, survivors can exhibit permanent disabilities, including cerebral palsy, mental retardation and epilepsy [1,2]. Brain lesions of early development include a wide variety of congenitally, perinatally, and postnatally acquired neuropathological conditions. Immature brain tissue necrosis is a common feature of these lesions, and the nature of the insult, the severity, and the period of development can lead to different types of lesions, such as: porencephaly cyst (PC), encephalomalacia, ulegyria (U), hemiatrophy, and leukomalacia [3,4]seizures, and mental retardation. The gestational age of the infant is one of the main variables determining the neuropathological picture of hypoxic-ischemic brain injury, and ulegyria (one of its neuropathological correlates. In vivo magnetic resonance imaging (MRI) allows to

distinguish between different patterns of brain lesions and to focus on specific rehabilitation and treatment to each distinct condition [5–7]. But, there is a lack of information regarding how brain lesions such as U and PC affect clinical outcomes such as activities of daily living (ADLs). In addition to the type and severity of brain lesions, the occurrence of secondary neurological deficits, such as epilepsy, can hinder normal function and performance during ADLs. Indeed, epilepsy is a common and highly prevalent feature after the HIE insult [3,5,8]. There is a growing evidence that U can lead to epilepsy due to cortical malformation obstructing neuronal and glial cells differentiation and synapses [9]. The great majority of epileptiform activity in conjunction with U incidence is classified as medically refractory, and frequently surgical removal of areas causing epilepsy is needed [3,10]seizures, and mental retardation. The gestational age of the infant is one of the main variables determining the neuropathological picture of hypoxic-ischemic brain injury, and ulegyria (one of its neuropathological correlates.

It is reasonable to think that better understanding the relation of U and PC with epilepsy incidence could improve rehabilitation and treatment prescription. We performed this study to verify a possible association between location, extension and severity of U and PC with ADLs. A better understanding of the possible relation between these variables can prove critical to gauging the efficacy of rehabilitative and treatment therapies to improve motor and functional independence. We hypothesized that type of lesion and epileptic status would positively correlate with motor and impairments to perform ADLs.

MATERIAL AND METHODS

SUBJECTS

The study involved 21 epileptic patients referred to the Epilepsy Center of the PUCRS Hospital, Porto Alegre/Brazil. Age at the time of our first observation ranged from 15 to 45 years (mean±S.D., 25.66±7.12 years). This study included patients with epilepsy characterized by recurrent seizures caused by U and/or PC, all examined by MRI to detect type of lesion, and EEG to detect epileptic status. All participants were screened according to the following inclusion criteria: 1) diagnosis of epilepsy secondary to hypoxic ischemic encephalopathy; 2) MRI-proven U and/or PC as described elsewhere [9]; 3) participants should be attending our Epilepsy Center during the study period; 4) patients should be cognitively able to answer Barthel Index (BI) questionnaire. Informed consent was obtained from all subjects. This study was approved by the Ethics Committee of our Institution (n.77309).

Anamnestic investigation was used to quantify and describe prenatal, neonatal and early childhood events. Epilepsy record was reviewed using medical records available at our Epilepsy Center.

IMAGING

Brain MRIs were performed in a 1.5 Tesla General Electric™ scan (Siemens AG, Erlangen, Germany). Imaging studies included volume acquisition, T1 and T2 weighted, and FLAIR sequences. Axial, coronal and sagittal sections were analyzed and interpreted by a blinded and experienced evaluator.

EEG

All of the patients underwent waking and sleeping electroencephalographic recordings made using the International 10-20 electrode

placing system (EMSA-BNT 36, Stellate System, Canada). Epilepsy was classified according to the type of crisis: simple partial crisis (SPC), complex partial crisis (CPC) and secondarily generalized crisis (SGC). The severity of epilepsy was defined using the type of seizure and seizure control method, as follows: I) complete surgical control (CSC); II) refractory seizures even with surgery (RSS) III) seizures completely controlled with antiepileptic drugs (SCCAD) and IV) refractory seizures even with antiepileptic drugs (RSAD).

MUSCULAR TONUS AND ACTIVITIES OF DAILY LIVING ASSESSMENT

In order to evaluate the muscular tonus we used the Ashworth scale [11]. Briefly, we tested the resistance to passive movement over joints using variable velocities. Ashworth's scale grades spasticity and the outcome ranges from 0 (normal muscular tone) to 4 (limb rigidity during flexion or extension). Other neurological disorders were also investigated, such as: dyskinesia, myoclonus, chorea, dystonia, tremors and ataxia.

We also used the Barthel Index (BI), to verify functional independence to perform ADLs as feeding, bathing, personal hygiene, dressing, among others [12]. This index consists of a 100-point rating scale of the ability to perform self-care and mobility tasks. For each task it is assigned a numeric value according to three levels of provided assistance (independent, assistance, dependent). Scores lower than 35 indicate complete assistance, scores ranging from 40 to 55 indicate partial assistance; scores ranging from 60 to 95 indicate minimal assistance to perform ADLs and scores higher than 95 indicate total independence.

STATISTICAL ANALYSIS

Descriptive statistics were used for quantitative and categorical variables. We used the Pearson's chi-square ($\chi 2$) or Fisher's exact test for comparing proportions among groups, $p < 0.05$ was considered significant. All statistical analyses were done using a software package (SPSS version 16.0, SPSS Inc.)

RESULTS

Twenty-one patients (15 males and 6 females mean±SD: 25.66±7.12 years) participated in this study. All patients had epilepsy associated with U and/or PC identified by EEG and MRI, respectively (Figure 1).

MRI analysis of brain lesions identified 71% (n = 15) of U lesions, 9.8% (n = 2) of PC lesions and 19.2% (n = 4) of combined lesions (ie., U and PC) (Table 1). Most of the lesions were located in fronto-centro-parietal (FCP) and occipital (O) brain regions. Ten patients (47.6%) presented associated injuries as hippocampal and cerebral atrophy, as described in Table 1.

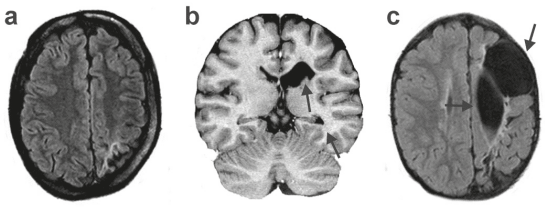

Figure 1. Brain MRI, sequences corresponding to lesion caused by (a) ulegyria (U), (b) porencephalic cysts (PC) and (c) both ulegyria and porencephalic cyst (U+PC).

Table 2 shows structural damage location and epileptiform discharges, considering the presence of irritative zone in one or more lobes of the brain. Seventeen subjects (80.9%) presented multilobar EEG electrical discharges and thirteen subjects (61.9%) presented epileptiform EEGs signals in regions adjacent to the site of structural damage. Regarding the type and seizure control, 10 patients (47.6%) had both SPC, CPC that evolved

Patient	Sex	Age (years)	Type of brain lesion	Location	Associated injuries
1	M	18	U	R FCP	R Brain atrophy + Brachicephaly + Microcephaly
2	M	20	U	Bilateral FCP	
3	M	37	PC	Periventricular L F	
4	M	22	U+PC	R FPC	Severe atrophy pre-splenial corpus callosum + R brain atrophy
5	M	15	U+PC	L FP extensive damage	L Brain and hippocampal atrophy
6	M	30	U+PC	L F	
7	F	23	U	L O	L Mild cerebral atrophy + cerebellar atrophy + megacisterna magna
8	F	19	U	Bilateral F	
9	M	21	U	Bilateral PO	
10	M	27	U	L CP	watershed lesion + L mild cerebral atrophy
11	M	30	U	R FCP	Multicystic encephalomalacia + R brain and hippocampal atrophy
12	M	19	U	R FCP	Hippocampal atrophy
13	M	36	U	R FPC	
14	M	39	U	L FPC	L Brain atrophy
15	F	28	U	L FCPT	L Hippocampal atrophy
16	F	30	U	Bilateral O	Splenium corpus callosum atrophy
17	F	26	U	L O	
18	F	36	U+PC	Bilateral P	
19	M	21	U	CP	Mild cerebral and cerebellar atrophy + L hippocampal atrophy + megacisterna magna
20	M	25	PC	L P	
21	M	17	U	Bilateral O	

Table 1. Type and location of brain lesion and associated injuries

Abbreviations: M, male; F, female; R, right; L, left; U, ulegyria; PC, porencephalic cyst; CP, centro-parietal; FCP, fronto-centro-parietal; F, frontal; FP, fronto-parietal; O, occipital; P, parietal; FCPT, fronto-centro-parieto-temporal

into SGC. Eleven (52%) patients underwent epileptogenic tissue removal and only one presented refractory epilepsy with recurrent seizures (data not shown). As shown on Table 3 we found no difference between type of brain injury (U and/or PC) and EEG features (e.g., slow/attenuation waves, epileptiform discharges, type of crisis, seizure focus location and associated disease).

Patient	Lobar discharges	Multilobar discharges
1		CPT
2		TP + R P
3		L F
4		R FC
5		FCT
6	F	
7	O	
8		R H
9		L TPO
10	P	
11		L FCPT
12		R FC
13		L FCP
14		L FC
15		L FC
16		Bilateral TPO
17		L TPO
18		L TPO
19	P	
20		Bilateral TO
21		Bilateral TO

Table 2. Location of epileptiform discharges

Abbreviations: M, male; F, female; R, right; L, left; F, frontal; O, occipital; P, parietal; TO, temporo-occipital; TP, temporo-parietal; TPO, temporo-parieto-occipital; CP, centro-parietal; CPT, centro-parieto-temporal; FC, fronto-central; FCT, fronto-centro-temporal; FCP, fronto-centro-parietal; FCPT, fronto-centro-parieto-temporal; H, hemisphere.

Comparison variables	P value
U/PC X EEG Slow Waves	0.6091
U/PC X EEG Discharge	0.6639
U/PC X Degree of Crisis Control	0.9806
U/PC X Type of Crisis	0.2869
U/PC X Discharges location	0.0609
U/PC X Associated injuries	0.2783

Table 3. Comparison of ulegyria and/or porencephalic cyst and EEG based epileptiform features.

Pearson's chi-square ($\chi 2$) test for comparing proportions, $p < 0.05$

Muscular tonus assessment showed 16 patients (76.2%) with abnormal tonus, 12 patients (85.7%) with spasticity, 2 patients (14.3%) with spasticity and ataxia. The most frequent distribution of limb impairment was hemiplegia (87%), followed by one case of diplegia and one case of quadriplegia (Table 4). BI score ranged from 30 to 95 points. Twelve patients (57%) needed partial assistance to perform ADLs, 4 patients (20%) required minimal assistance and 5 patients (23%) needed complete assistance to perform ADLs. Combined U and PC lesions resulted in significantly **lower BI scores,** when compared to U patients ($p < 0.05$).

DISCUSSION

A deeper understanding of how HIE relates to distinct brain lesions that can lead to epilepsy and hinder ADLs is critical to prescription of rehabilitative strategies and treatment of symptoms. In the present study we analyzed the association between location, extension and severity of U and/or PC with epilepsy and the ability to perform ADLs in patients with HIE. Frequently, patients that suffered perinatal HIE develop epilepsy during the first years of life. Long term outcomes, such as motor impairments which impact performance of ADLs, can be related to lesion type, severity of motor deficits and

Patient	MT	Topographical distribution	BI score
1	Sp (2)	L H	50
2	Sp (2)	L H	45
3	Sp (4)	DIPL	40
4	Sp (3)	L H	35
5	Sp (3) + atax	R H	30
6	Sp (2)	R H	45
7			50
8	Sp (4)	QUADR	30
9			90
10	Sp (1)	R H	55
11	Sp (1)	L H	55
12	Sp (2)	L H	50
13	Sp (2)	L H	55
14	Sp (2)	R H	50
15	Sp (1)	R H	50
16			90
17			85
18	Sp (3)	L H	35
19	Sp (1) + atax	R H	50
20	Sp (3)	R H	30
21			95

Table 4. Muscular tonus and level of independence for activities of daily living

Abbreviations: MT, muscular tonus assessed by Asworth scale; H, hemiparesis; DIPL, diplegia; QUADRI, quadriparesis; R, right; L, left; BI, Barthel index; Sp, spasticity level; Atax, ataxia.

epileptic status [13]. Reports of U and/or PC are scarce in the literature, and could be an interfering factor when analyzing functional and motor outcomes in patients affected by HIE. Additionally, information about the clinical manifestation, course, treatment, and prognosis is lacking. Suggesting that a possible link between lesion type, epileptic status and motor/functional outcomes should be better analyzed and understood. Although no significant correlation was found between these variables, we report an increased functional deficit in subjects that presented a combination of both types of lesion, i.e., U and PC. Therefore, early diagnosis of U and PC is important to increase chances of better response for drug therapy or surgical treatment, as well as, refer patients to psychomotor therapy programs to improve functional recovery.

Brain lesions caused by U and/or PC can occur at any brain regions, however, it is usually most marked in the posterior regions at the border zone of the three major cerebral vessels [3,9,14]. In this study, U and/or PC lesions affected mostly the fronto-centro-parietal areas followed by occipital brain regions. These data confirmed the high incidence of patients with motor disorders resulting from lesions in the primary motor cortex [15,16]because of the difficulties involved in designing and implementing feasible studies. The lack of data supporting the therapeutic usefulness of surgery precludes making strong recommendations for patients with epilepsy. We conducted a randomized, controlled trial to assess the efficacy and safety of surgery for temporal-lobe epilepsy.\\n\\

nMETHODS:Eighty patients with temporal-lobe epilepsy were randomly assigned to surgery (40 patients. Consequently, most of the patients presented spastic hemiplegia that increased assistance to perform ADLs, especially in combined lesions (ie., U and PC) patients where these deficits were increased. Importantly, since most of the patients needed partial assistance to perform ADLs, we assumed that this outcome might be related to spasticity and not to seizure control, once the majority underwent resective epilepsy surgery.

We did not find any association between the extent of lesions in brain MRI and the epilepsy severity, regardless of brain injury type (i.e., U and/or PC). Although the lesions identified on brain MRI are localized, the EEG discharges may occur in regions adjacent to the structural lesion. In other words, the structural damage identified by MRI should be understood as the structural locus of brain damage which becomes less visible on adjacent MRI scans, but the functional impairments can persists to the surroundings of this structural core. [17–19]which results from a perinatal ischaemic brain injury. It presents with a characteristic gyral pattern: small circumvolutions with atrophy at sulci bottom and spared apex. Ulegyria is frequently associated with epilepsy, cerebral palsy and mental disability. We analysed electroclinical and MRI features in patients with ulegyria and epilepsy. PATIENTS AND METHODS We reviewed 25 patients (14 males/11 females. The epileptiform relation to brain lesion types could be better understood using more detailed EEG analysis (video-EEG and invasive video-EEG recording), not accomplished in the present study.

We highlight the relevance of this study over the fact that there are a substantial number of individuals diagnosed with cerebral palsy (HIE) that present U and/or PC associated with intractable epilepsy, motor and functional deficits. Thus, a better understanding of how these features relate to each other can shed a light upon new treatments that might improve quality of life of those patients. In fact, the lesion extension in the 'brain paralysis' is static, but motor performance is worsened with time, due to the lack of voluntary movement, stiff muscles and joint deformities imposed by spasticity and impaired motor control. Antiepileptic drugs and surgical control of seizures associated to physical and cognitive rehabilitation my lead to a refining and remodeling of pre-existing patterns which likely will result in greater functional independence and better quality of life. Altogether, our data highlight the debilitating effect of combined U and PC lesions on functional outcomes, such as ADLs. We strongly suggest that both early diagnosis of HIE and early intervention will promote impacting changes in performance of ADLs and consequently improve quality of life for this patients.

We did not assessed issues related to cognition, behavior and visual capacity of these subjects that might be considered a methodological limitation of the study. Another limitation is the lack of the functional neuroimaging studies (SPECT and PET) considering the presence of irritative zone in one or more lobes of the brain.

CONCLUSIONS

HIE is frequently associated with cortical brain lesions such as U and/or PC, epileptiform activity and motor deficits. Understanding how lesion type, local and type of epilepsy and functional outcomes relate can help doctors and rehabilitation professionals evaluate surgical, pharmacological, physical therapy, speech therapy and order interventions according to each patient's needs. In the present study there was no association

between location, extension and severity of U and/or PC with epilepsy features. On the other hand, U and/or PC lesions were associated to motor impairments that harmed functional independence to perform ADLs. Interestingly, a combination of these lesions reduced the ability to perform ADLs.