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Diagnostic methods for extra-temporal neocortical focal epilepsies

Present and future

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ABSTRACT

The progress of epilepsies diagnosis has been great, but, amongst the diagnostic detailing that demand research, one of the most important is the essential lateralization and localization of epileptogenic zone, considered as the cerebral cortex region, that removed, will result in a free state of seizures. The present study aims to analyze the possible uses of proton spectroscopy for clinical and pre-surgical evaluation of focal extratemporal epilepsies, since this group presents the highest difficulty degree for lateralizing and locating epileptogenic zones. In almost all cases, a non invasive diagnosis can be performed using routine electroencephalography, video-electroencephalography - considered as gold standard, and magnetic resonance imaging. However, when the results of these exams are contradictory, some patients need invasive techniques, as the intra-cranial video-EEG, using deep electrodes, sub-dural strip and grid, that are associated with increased diagnostic cost and risk of complications, as cerebral hemorrhages and intra-cranial infections. Proton spectroscopy appears as a possibility, given its capacity to evaluate cerebral metabolism, by N-acetyl-aspartate (NAA), creatine (Cre) and choline (Cho) concentrations, amongst other metabolites. This non invasive method may provide time reduction of this evaluation and reliable level improvement for this topographical diagnosis.

Key words: extratemporal neocortical epilepsies, diagnostic methods, magnetic resonance spectroscopy, pre-surgical evaluation.

Métodos diagnósticos das epilepsias focais neocorticais extratemporais: presente e futuro

RESUMO

Tem sido grande o progresso no diagnóstico das epilepsias, mas dentre os detalhamentos diagnósticos a exigir pesquisas, estão a lateralização e a localização precisas da zona epileptogênica, considerada como a região do córtex cerebral que, removida, irá resultar num estado livre de crises. Por meio de revisão da literatura, o objetivo deste estudo é expor e analisar os métodos diagnósticos das epilepsias neocorticais extratemporais, dadas as características que as tornam mais complexas do que as epilepsias temporais visto que estas apresentam o maior grau de dificuldade para lateralização e localização das zonas epileptogênicas. Na maior parte dos casos, o diagnóstico pode ser firmado de forma não invasiva, empregando-se a eletrencefalografia de superfície, a vídeo-eletrencefalografia, considerada o padrão-ouro, e a imagem por ressonância magnética. No entanto, quando os resultados dessas investigações são contraditórios, alguns pacientes necessitam de técnicas invasivas, como o vídeo-EEG intracraniano, utilizando eletrodos profundos, placas ou estrias subdurais, que se associam ao aumento do custo diagnóstico e do risco de complicações, como as hemorragias cerebrais e as infecções intracranianas. A espectroscopia de prótons surge como uma possibilidade, dada sua capacidade de avaliar o metabolismo cerebral, por meio das alterações de N-acetil aspartato (NAA), creatina (Cr) e colina (Co), dentre outros metabólitos. Esse método não invasivo pode reduzir o tempo de avaliação e melhorar o nível de confiança desse diagnóstico topográfico.

Palavras-chave: epilepsias neocorticais extratemporais, métodos diagnósticos, espectroscopia por ressonância magnética, avaliação pré-cirúrgica.

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Epilepsy is a group of neurological diseases, that share the presence of abnormal, unprovoked, repetitive, excessive brain electrical discharges with clinical manifestations named epileptic seizures, with neurobiologic, cognitive and social consequences, because they are associated to comorbidities[1-5]. The comorbidities, progressive or not, may include: knowledge disturbances, permanent neurological deficits, as well as psychological and psychiatric problems[3].

Epilepsy risk factors vary according to age and geographical development level, that seems to explain great variability of prevalence and incidence rates[3]. According to some world studies, the annual general incidence of epilepsy varies from 24.0 to 82.0 per 100,000 habitants/year, but it is influenced by the country's development level. In industrialized countries, the incidence ranges from 40 to 70:100,000 habitants/year, but it is greater in poorer countries[9]. In Latin America, amongst 2,895 published studies from 1987 to July 2004, according to three studies included in a systematic review[6], the incidence per 100,000 habitants/year varied from 77.7, at Martinique's Islands, to 190.0, in Ecuador. Considering the incidence related to age, it is major on first year of life, decreases during infancy (varying from 83.0 to 87.0 per 100,000 habitants/year) and has its lowest rates between 20 and 39 years old; rises substantially from the sixth decade, reaching the highest value at the seventh decade[1,7-9.]

The prevalence in industrialized countries vary from 4 to 10 per 1,000 habitants/year, but the epidemiological studies are extremely controversy due to the great methodological variability[3,7]. In Europe, active epilepsy prevalence varies between 3.3 and 7.8 per 1,000 habitants/year[9]. In Latin America, amongst 1,713 published studies from 1987 to July 2004, 32 were considered in a systematic review of epilepsy prevalence. Although the general prevalence was equal to 17.8 per 1,000 habitant/year, an interval from 6.0 to 44.3 was detected[6]. In Brazil, the variability interval was 11.9 to 18.6 per 1,000 habitants/year[1,6].

Due to the epidemiological dimension and the social impact, epilepsy is considered a public health problem of difficult solution, because even the diagnose is a challenge. Until 1970, epilepsy diagnose was not systematized; there were many attempts to classify the diagnoses and to standardize epilepsy seizures and syndromes terminology. On 2001, the International League Against Epilepsy (ILAE) Task Force on classification and terminology proposed the diagnostic scheme for people with epileptic seizures and with epilepsy, recommending five diagnostic Axis[4,5,10].

To restrain the objective of this article - extra-temporal neocortical focal epilepsies, it is important to point out some details of this classification. On Axis 2, related to seizure type, focal seizures, different from generalized ones, are generated by a localized neuronal dysfunction or by the dispersion of electrical discharges to other brain areas, due to the excitation of neuronal net[2-5,10,11]. On Axis 3, the main criteria to classify epileptic syndromes, are clinical presentation and neurophysiologic and image findings. One must emphasize some characteristics of symptomatic syndromes, that is, those with defined etiology, as well as probably symptomatic, prior named as cryptogenic due to the plausibility of an etiological agent, even though its existence has not been identified. Both are subdivided as: limbic (specially the mesial portion of temporal lobe) or neocortical[10-14].

This article focuses focal epilepsies, symptomatic or probably symptomatic, neocortical (except Rasmussen syndrome), of extra-temporal localization, whose diagnose requires necessarily the localization and the lateralization of epileptic zone, and this is the challenge. Actually neurophysiological and image exams brought a new perspective to epilepsy carriers concerning diagnose, treatment and follow-up.

The objective of this review is to expose and to analyze the diagnostic methods of focal neocortical extratemporal epilepsies, due to their more complex characteristics when compared to temporal epilepsies.

Electroencefalography

Technological progress allows the use of four electroencephalographic techniques (EEG) for the diagnoses of epilepsies: surface EEG on 10-20 systems, EEG on 10-10 system, video-EEG with the association of electroencephalographic register to that of clinical seizures; stereo video EEG, that differs from video EEG because of the insertion of deep electrodes inserted directly in encephalic cortex, by stereotaxic surgery[15], and electrocorticography.

Surface electroencephalography is an essential method for diagnose, characterization and localization of extratemporal neocortical epilepsies, nevertheless it has low sensibility compared to identical application for temporal epilepsies[16]. Thus, for frontal epilepsies, false lateralization and the presence of generalized discharges, which in fact are the result of a secondary bilateral synchronization, imply on an important limitation to identify the real lateralization of epileptic zone. Concerning to epilepsies of parietal lobe, the evaluation and localization of epileptic discharges by surface EEG are very difficult, and this determines the impossibility to explicit localization or even to define a false lateralization. For epilepsies of occipital lobe, the difficulty of lateralization is added to a diffusion of discharges, in many cases, to ipsilateral temporal lobe with clinical manifestations similar to those of temporal lobe[17].

Due to diagnostic limitations of surface EEG, especially for extratemporal epilepsies, video-electroencephalography constitutes an extremely efficient method for diagnose and localization of epileptic zones. It is able to characterize even primary and secondary epileptic zones

and dispersion areas. Although it constitutes a more accurate method than surface EEG, it has minor diagnostic sensibility to extratemporal neocortical epilepsies than to temporal ones[18].

This diagnostic limitation of EEG and video EEG is still more evident as therapeutic surgery for epilepsy is been more frequent, derived from the necessity to an accurate localization of epileptic zone to be excised. That is the reason for electrocorticography use.

Electrocorticography is a method that analyzes the synchronization of post synaptic potentials of primary occurrence on pyramidal cells of cerebral cortex, without the interference of physical ways as cerebrospinal fluid, arachnoid membrane, dura mater meninges, skull bones and scalp subcutaneous tissue. For this reason, it is a more sensible method for the localization of epileptic zone than surface EEG, because it is independent of amplitude variations of electrical potential and has a good spatial resolution[19-21].

Imaging diagnoses: the present

Currently, imaging exams offer a new perspective for diagnosis, treatment and management of epilepsies. It is necessary to analyze its contribution to these processes, as well as to the localization and lateralization of epileptic zone on extratemporal epilepsies. Among these methods, one must emphasize: computerized tomography, magnetic resonance imaging, functional magnetic resonance, positron emission tomography and single photon emission tomography.

Around 1970, computerized tomography has revolutionized neurological diagnose by permitting the visualization of brain structures safely and with better images, and started been considered as the best imaging method for neurological diagnose[22]. It is ideal to detect and evaluate the extension of intracranial calcifications within cists, neoplasias, Sturge-Weber syndrome, cerebral hemorrhages and head trauma, among other indications[11,13,23].

Although being very employed in emergency rooms due to short performance time and low cost when compared to other imaging methods, computerized tomography has not well defined criteria to help diagnose or influence prognosis of epilepsies, as well as it has a high cost/benefit rate, derived from scarce financial incomes for health sector in our country[24]. Besides this fact, this exam has low sensibility for the diagnose of primary structural cerebral lesions present in epilepsies, and is considered as a secondary or supplementary diagnostic method to others more accurate[11,13,23].

Magnetic resonance imaging (MRI) revolutionized neuroimaging, since the end of 70's and the beginning of 80's, and it is considered the best non invasive method to evaluate the brain structure[11,24]. It is the elective method for drug resistant epilepsies with surgical indication, because it presents high sensibility and specificity for lesions like tumors, neuronal migration disturbances (especially dysplasias), hypoxic ischemic injuries, infections, born inherited metabolic errors, trauma, neuro-cutaneous diseases, vascular malformations, gliosis, among others[3,11,13,23]. Nevertheless, the advent of surgery for treatment of epilepsies arouse the necessity to investigate new methods for therapeutical planning.

Technological advances in imaging diagnose permits functional analysis by the activation of eloquent areas of brain, evaluated by blood flow increase with no association to oxygen consumption, suggesting anaerobic metabolism during activation. Functional magnetic resonance is based on the evaluation of difference on oxygen concentration on capillary and blood veins, at activated areas, compared to those not activated, expressed by a difference on signal intensity. This difference is employed to generate a functional map[1,3,13,25], whose superposition to anatomical structure allows the identification of areas associated to motor, sensorial and cognitive functions[26].

For extratemporal epilepsies, functional magnetic resonance associates the encephalic structural study to functionality of its structures, which confers an important gain for neurological surgeries. Although this exam does not permit localization and lateralization of epileptic zone and, therefore, one must use other functional methods.

Single photon emission computerized tomography (SPECT) is the functional imaging technique most used for epilepsies. This method turns possible the visualization of drugs distribution according to cerebral blood flow, identifying high perfusion at epileptic zone within ictal period, and, thus, showing its difference from interictal and post ictal periods[3,25].

Positron emission tomography (PET) uses fluorodeoxyglucose (FDG) as glucose metabolic marker, allowing the identification of epileptic zone by the reduction of metabolism within the correspondent area. For metabolic evaluation, its functional characteristic, it is ideally performed within ictal period, when metabolic velocity is higher and epileptic zone may be more clearly distinguished. Due to the fact that marker is rapidly metabolized, in most of cases, the exam is performed on interictal period, with loss of sensibility derived from a lightly labeling of epileptic zone[25,27,28]. This loss of sensibility is still major for extratemporal epilepsies than for temporal epilepsies, mainly because a rapid diffusion of abnormal electrical activity for neighboring areas may represent a confounding factor derived from tagging other sites than epileptic zone[11,25,27,28].

Despite the diversity of imaging methods, one gap persist for diagnose and therapeutic management of patients with neocortical extratemporal epilepsy causing a difficulty for control of seizures. The researchers are focusing functional methods with major sensitivity than static methods. Among those functional methods, the fu-

ture points out for magnetic resonance by diffusion tensor, fiber tractography and protons spectroscopy.

Imaging diagnose: the future

Diffusion tensor magnetic resonance imaging (DT-MRI) and fiber tractography have been considered actually as highly promising for the investigation and pre-surgical evaluation of neocortical extratemporal epilepsies[29-32].

DT-MRI is a non invasive technique that employs *in vivo* 3D quantitative measures of water passive diffusion for the orientation of axon fibers in the white matter. The movement of water molecules in brain is limited by structures like axons and myelin and their diffusion has the standard orientation of cerebral fibers, due to course or anisotropy. The dominant orientation and the diffusion magnitude may be quantified by vector and diffusion value, respectively, obtained by diffusion tensor measure. These informations are codified by colors and vector maps. Diffusion tensor allows the construction of functional anatomic map, named fiber tractography, with identification of afference and efference on brain tracts. This analyses permit surgical planning and the pre-selection of better abroad for lesionectomy[33].

Another diagnostic method for neocortical extratemporal epilepsies, with great perspectives for future, is magnetic resonance spectroscopy (MRS), which represents the non invasive major advance on *in vivo* research of brain metabolism[33-38].

MRS and MRI apply the same physic principles, differing only on the way they process and show data. Within MRI, we can obtain anatomical images, while MRS generates a graphic that represents some encephalic metabolites invisible on MRI[39].

MRS may be obtained by different atoms as hydrogen (^{1}H), phosphorus (^{31}P) and carbon (^{13}C). For clinical objectives, the atom most used is hydrogen derived from its abundance in organism and also to its higher signal. The brain metabolites, that can be detected, are exclusively those in whose molecule ^{1}H protons is present on a concentration major than 0.5 mMol/L. As water concentration is at least 100 times major than metabolites concentrations, it is necessary the suppression of ^{1}H peak, so brain metabolites may be visualized[40].

On the evaluation of $1H^{+}$ MRS graphic, each metabolite is identified by the specific peak localization on the abcissa axis, and its concentration, on parts per million (ppm), is obtained by the area under each curve, calculated automatically by the engine[41].

After the acquisition of a MRI sequence, one initializes $1H^{+}$ MRS technique, choosing and delimitating a brain region, named voxel, where the biochemical evaluation will be performed. According to the voxel, $1H^{+}$ MRS is technically classified as single voxel or multiple voxels. Single voxel technique provides also a single graphic that represents the metabolic activity of the whole brain volume analyzed, preferentially with 8 cm^{3}, while within multiple voxels technique, it is possible to obtain the correspondent graphics of different regions of brain lesion and also of the contralateral brain tissue, because the focalized volume can be divided into small subvolumes[42].

Another physical parameter of $1H^{+}$ MRS is the echo time (ET). With a long ET (major than 100 ms), it is possible to identify four metabolites (N-acetyl-aspartate, creatin, choline and lipid-lactate) (Fig 1A). With short ET (approximately equal to 30 ms), besides those metabolites, two other are detected: myo-inositol and glutamine-glutamate (Fig 1B)[39,40,43].

The exam interpretation consists on the spectral anal-

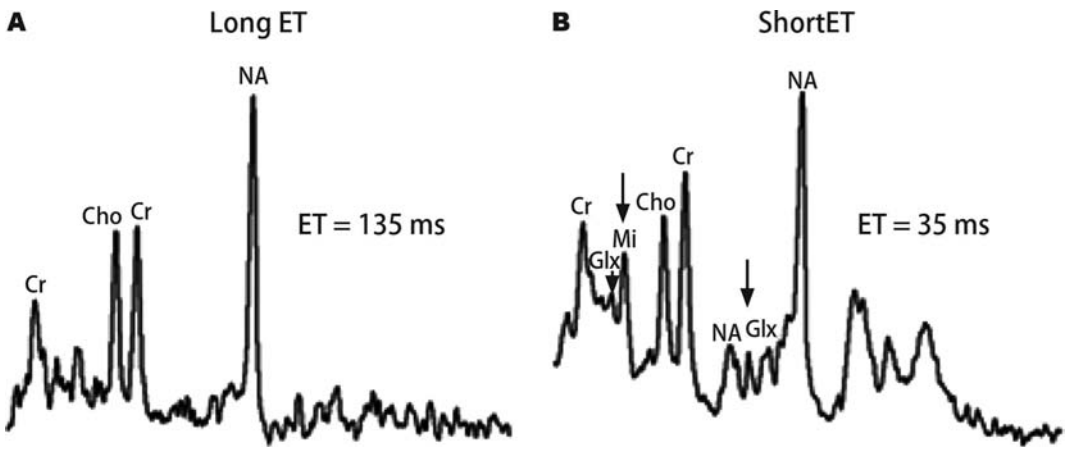

Fig 1. Differences on hydrogen protons spectroscopy graphs of normal patients, with Long ET and Short ET. [A] With Long ET, one can identify three metabolites (NAA, Cho, Cr). [B] With short ET, besides these metabolites, two more are identified: Mi e GLX.

Table. Cellular meaning and localization of the main metabolites identified by hydrogen protons spectroscopy.

Metabolite	Cellular meanings of metabolites	PICK (ppm)	
		First	Others
NAA – N-acetyl-aspartate	Marker of number and viability of neurons	2.02	2.6
Cr – creatine	Markers of systems of energy of encephalic cells	3.03	3.9
Co – choline	Membrane markers It is related to cell membrane production and destruction High concentrations indicate hypercellularity and myelin destruction	3.2	–
Lac – lactate	Absence in normal tissue High concentrations indicate fault of cellular oxidative respiration	1.32	–
Lip – lipids	Necrosis marker (high grade tumors)	0.8	1.2–1.5
GLX – glutamine-glutamate	Neurotransmitter, neuroexcitator, detoxificator and regulator of neurotransmission activity	a – 3.65 a 3.8 b – 2.05 a 2.5	– –
mI – mio-inositol	Osmolite (osmolar regulator of cell volume) Glial marker	3.56	–

Adapted from Danielsen and Ross[39].

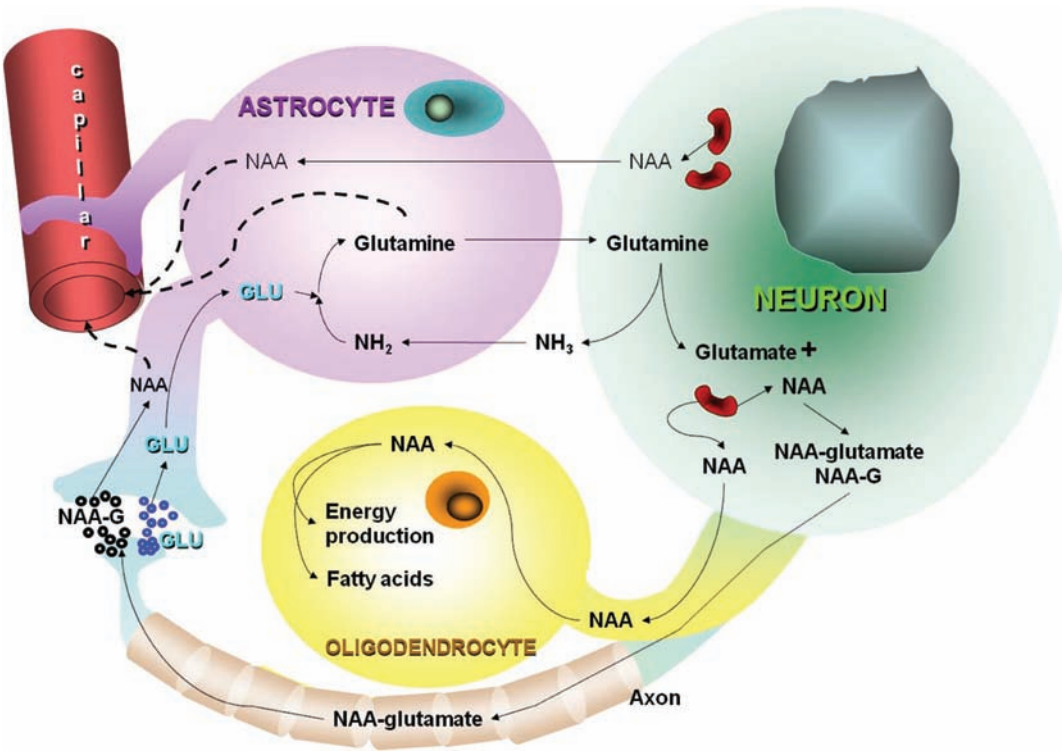

Fig 2. Metabolism of N-acetyl-aspartate in central nervous system. NAA: N-acetyl-aspartate; GLU: Glutamate; NAA-G: NAA glutamate; NH3: amone grouping; NH_2: amine radical. Adapted from Moffet et al.[49].

yses, made by visual or computed inspection. Visual inspection demands normal spectrum knowledge to recognize abnormal spectrum by the relations among metabolites length, originating a subjective classification. Computed analyses permits a relative quantitative evaluation, because the software compares the area under the curve correspondent to each metabolite to that of a standard metabolite, that is generally creatin (Cr), because this one is considered by many authors as the most stable for various central nervous system diseases[39,44].

On Table, the interpretation at cellular level of the principal metabolites identified by $1H^+$ MRS are presented.

To explain the clinical meaning of the alterations on brain metabolites concentration determined by $1H^+$ MRS,

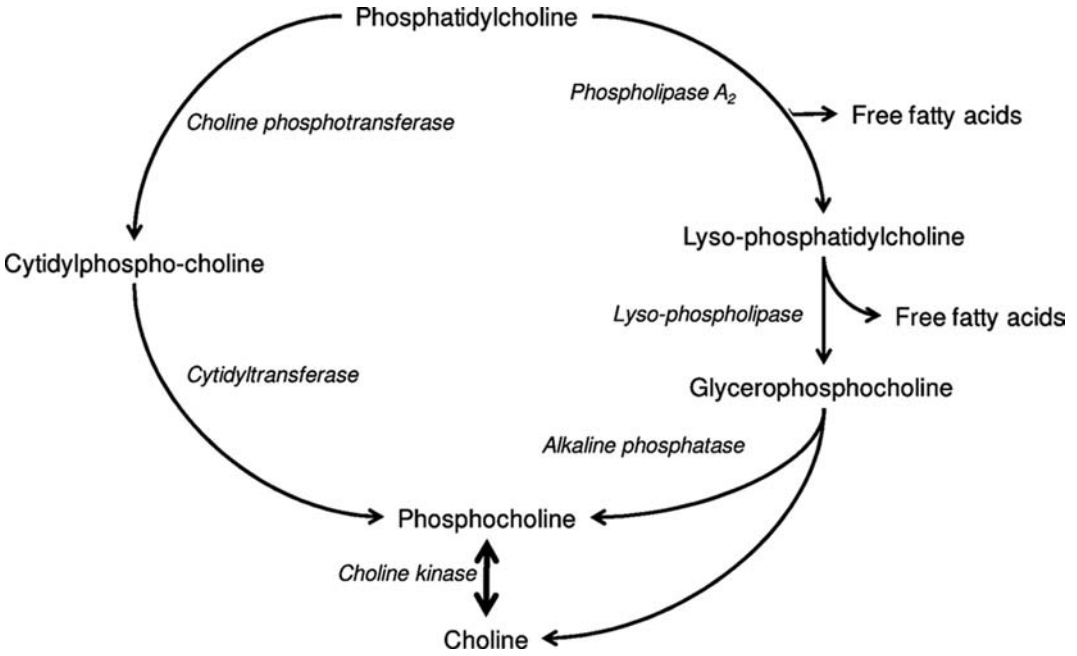

Fig 3. Metabolism of choline in central nervous system (Adapted from Klein[51]).

in extratemporal neocortical epilepsies, some aspects of brain metabolism of N-acetyl-aspartate, choline and creatine are essential[45-47].

NAA is synthesized in neuronal mitochondria and may be transported to oligodendrocytes, for the synthesis of fat acids and and energy production within tricarboxilic acids cycle, or may be used for the synthesis of N-acetyl-aspartilglutamate (NAA-G) in neurons[48].

Glutamine, present into the astrocytes, are converted in glutamate, by deamination, which, into the neuron, links to NAA, converting into N-acetyl-aspartilglutamate, that is liberated into neuronal synapses with others excitatory neurotransmitters, as excess of glutamate. Into extracellular environment, NAA-G is hydrolyzed by glutamate-carboxipeptidase II, generating NAA, which diffuses into astrocytes, and the glutamate may be converted in glutamine, by the molecular incorporation of ammonia radical, under the action of glutamine-synthetase. NAA synthesized by neuronal mitochondria or derived from the dissociation of NAA-G, with the presence of an excess of brain nitrogen, is excreted by blood capillary of central nervous system, together with the excess of glutamine[49] (Fig 2).

As a result of this metabolism, the NAA exerts, into CNS, two functions: the facilitation of energy metabolism by neuronal mitochondria and the synthesis of fat acids and steroids, by acetate path, into oligodendrocytes. In other words, the NAA express the celularity and the neuronal metabolic hability[50].

Another brain metabolite largely studied is choline, the molecule that integrates a cycled path, by which it is a phosphatidylcholine catabolite, as well as its anabolite. Within a normal physiologic condition, this path can maintain choline and phosphatidylcholine adequated concentrations, by the conversion of one into another. Phosphatidylcholine is degraded by phospholipase A_2, into free fat acids and liso-phosphatidylcholine, that may be reconverted into phosphatidylcholine, or degraded by liso-phospholipases into free fat acids and glycerophosphocholine. The glycerophosphocholine may follow two different metabolic paths: the conversion into phosphocholine, due to the action of alkaline phosphatase, or into free choline[51]. Phosphocholine can be converted into free choline by cholinokinase, or into citidylphosphocholine, under the action of choline-transferase, and lately into phosphatidylcholine, by cholinephospho-transferase, closing the phosphatidylcholine – choline metabolic cycle[52] (Fig 3).

Phosphatidylcholine is the most frequent phospholipid of eucariot membranes and represents 40% of its composition. In pathologic processes that break membranes, its concentration rises and promotes also a higher concentration of its degradation products, among which is choline. Due to this metabolic path, a higher choline concentration represents membrane destruction, and its reduction, the synthesis of membranes (that is the cellular turnover)[53].

The third metabolite of interest for the present study is creatine, a molecule involved on cellular energy storage, as phosphocreatine. For this reason, high concentrations of creatine express neuronal ability to storage energy (as phosphocreatine), and creatine reduction represents energy consumption[54,55].

Epileptic patients may have the NAA concentration reduced due to a higher energy consumption, wasted for electric discharges, by neuronal dysfunction, or, even, by neuronal lesion[34,38]. Nowadays, a hypothesis admits that the raise of mitochondrial energy consumption promotes a reduction of neuronal synthesis of NAA, and, therefore, an increase of glutamate (its precursor), that promotes, in normal individuals, a major synthesis of γ-aminobutiric acid (GABA), that is an inhibitory neurotransmitter. The major energetic consumption occurs in an intermittent way, depending on physiologic needs, and so GABA also suffers variations along the day. Differently, in epileptic patients, it seems happen a disequilibrium of glutamine, glutamate (excitatory neurotransmitters) and GABA[49], due to scarcity of glutamate transferase, and not to lack of substrate[56].

The Cr pick is generated by phosphocreatine and creatine metabolism and it indirectly reflects the energetic metabolism. This fact explains why creatine is mostly used as the reference pick for signal intensity of normal metabolism. The signal of choline is generated by glycerophosphocholine, phosphocholine and free choline, as part of cellular membrane degradation and synthesis[34].

The researches on epilepsy aim to identify the relation between the alterations of these metabolites and the modifications shown on EEG, on video-EEG, and on MRI, to establish diagnostic patterns of localization and lateralization of epileptogenic zones. Studies performed with normal individuals did not found brain assimetries right-left type and the patterns of NAA, Cho and Cr metabolites distribution, characteristic of each brain region[34]. Although, on video-electroencephalography and stereo-videoelectroencephalography of extratemporal neocortical epilepsies, a reduction of NAA, and also of NAA/Cr, NAA/Cho and NAA/Cr+Cho have been informed on the epileptogenic zone side, when compared with the opposite side[35,38,57].

Within the last four decades, without doubt, technologic advances have contributed very much to epilepsies diagnose, but they are still insufficient to attain all the prognostic objectives. For this reason, the studies have been intensified using proton spectroscopy and researches determined as a priority the analyses of brain metabolism. These findings point out the possibility that spectroscopy, in future, may constitute one more exam integrating the arsenal for diagnose of epilepsies as well as for therapeutic planning strategies.

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