Presentación de trabajos de plataforma

Presentation of platform sessions

Saturday 3rd July 2004
12:30 - 13:30

1
MRI VOXEL-BASED-MORPHOMETRY IN PATIENTS WITH IDIOPATHIC GENERALIZED EPILEPSIES

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PURPOSE: Idiopathic generalized epilepsies (IGE) are a group of frequent epileptic syndromes. These age-related syndromes are clinically characterized by generalized tonic-clonic, myoclonic and absence seizures. Five main subsyndromes are described according to predominant seizure type and age of onset: childhood absence and juvenile absence epilepsy (AE), juvenile myoclonic epilepsy (JME), generalized tonic-clonic seizures on awakening (GTCS-A) and IGE with tonic-clonic seizures alone (TCS). Visual assessment of routine magnetic resonance imaging (MRI) in patients with IGE is normal in almost all patients. However, quantitative evaluation is increasing the sensitivity of brain MRI. Studies showed that cortical gray matter volumes are significantly increased in patients with IGE when compared with controls. Voxel-based-morphometry (VBM) uses automatically segmented cerebral gray matter for comparisons. This method eliminates the investigator bias and reduces the interaction time between the investigator and the computer. The purpose of this study is to investigate the neuroimaging features in patients with IGE using VBM.
METHODS: We studied 150 individuals (38 controls, 54 with JME, 21 with AE, 6 with GTCS-A and 31 with TCS). Classification was made according to clinical and electroencephalographic criteria (ILAE, 1989). The control group was composed by healthy individuals. The volumetric (3D) T1 GRE sequence acquired in a 2.0T MRI scanner was used for analysis. VBM was performed searching for increased gray matter concentration (GMC) in all IGE patients and IGE groups individually in comparisons to controls.
RESULTS: Comparison between controls and all patients with IGE showed areas of increased GMC located mainly in the regions of superior frontal cortex and basal ganglia. When comparing JME patients and controls, increased GMC was found predominantly in basal ganglia and thalamus but also in frontobasal and frontomesial regions. Comparisons between the groups GTCS-A and TCS individually with controls showed increased GMC areas in frontal motor, basal ganglia and insula. Patients with AE showed increased GMC in the frontoparietal region.
CONCLUSIONS: Patients with IGE have increased GMC located mainly at the frontal lobe and basal ganglia. Individual comparisons showed that patients with JME had a more widespread GMC increase compared to other forms of IGE. The similar pattern presented by patients with GTCS-A and TCS suggests a similar pathophysiological mechanism in these two forms of IGE. In patients with AE, the predominant abnormality was more posterior than in the others types of IGE.

2
DNA DISTRIBUTION IN HUMAN KINDLED NEURONS

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PURPOSE: Neurogenesis in normal human neurons has been described recently, as has DNA studies in kindled neurons. Nevertheless, such procedures have included small amounts of cells that have been processed with biased and subjective methods. We have determined neurogenesis, measured by "S" phase determinations, in thousands of normal and kindled human neurons, using flow cytometry, which is a computerized and unbiased method.
METHODS: Paraffin embedded tissue samples from epileptogenic foci from 20 patients, as well as from 20 cadaveric brain tissue samples were processed as cell suspensions for flow cytometry. Cell cycle neuronal phases were obtained through nuclear size selection. "S" phase nuclei from kindled neurons were compared with "S" phase

nuclei from neurons obtained from similar cerebral area in normal cadaveric samples. Statistical analysis of the results was made using independent paired sample analysis.

RESULTS: There was a statistically significant increase in "S" phase nuclei in samples obtained from human kindled neurons compared with neuron samples from normal cerebral tissue ($p \leq 0.01$). We also obtained a neurogenesis rate from kindled human neurons as well as normal human neurons, using a greater am mount of cells.

CONCLUSIONS: "S" phase from human neurons can be obtained as a neurogenesis rate using flow cytometry analysis. Neurogenesis is greater in kindled neurons compared with normal cells with statistically significance of $p \leq 0.01$.

3

NEW PROTEINS CONFIGURE A BRAIN PHARMACORESISTANCE MAP IN TUBEROUS SCLEROSIS (TS)

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PURPOSE: TS is an autosomal dominant syndrome characterized by seizures that are refractory to medication in severe affected individuals. Recently, we described the high expression of both multidrug resistance MDR-1 and MRP-1 proteins in brain epileptogenic cortical tubers (ECT) of patients with TS and refractory epilepsy (RE) [Lazarowski et al. *Pediatr Neurol* 2004; 30(2): 102-6]. New pharmacoresistance proteins have been described in different tumors. The breast resistance cancer protein (BRCP) was first described as a membrane protein in breast cancer, and the lung resistance protein also known as mayor vault protein (LRP/MVP) was first described as a cytoplasmatic protein in lung cancer. Both proteins confer multidrug-resistance phenotype to the tumors. We describe the expression of both BCRP and MVP/LRP proteins in ECT from 3 patients with TS and RE.

METHODS: We investigate retrospectively the BCRP and MVP/LRP proteins on the same brain specimens that previously described the MDR-1 and MRP-1 expression. BCRP and MVP/LRP were studied by immunohistochemistry using specific monoclonal antibodies.

RESULTS: BCRP was present in 3/3 cases, and only detected in vascular endothelial cells (VEC) from all the vessels examined, but not in other brain parenchyma cells. MVP/LRP was present in 1/3 cases, and only expressed in several but not all ballooned cells.

CONCLUSIONS: The expression in ECT of: a) BCRP on vascular endothelial cells , b) MDR-1 and MRP-1 in VEC, astroglia, microglia, neurons and ballooned cells, c) MVP/LRP in ballooned cells, configure a brain protein pharmacoresistance map from patients with TS and R.

4

CHANGES IN CATECHOLAMINES AND AMINO ACIDS PATHWAYS IN PATIENTS WITH INTRACTABLE TEMPORAL LOBE EPILEPSY

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PURPOSE: Temporal Lobe Epilepsy (TLE) comprises 40% of epilepsies. The main aim of the present study was to investigate whether catecholamine and amino acid neurotransmission in specific brain regions plays a role in the regulation of seizures in TLE patients.

METHODS: Nine patients with TLE and 2 patients with temporal lobe tumor were submitted to surgery. Fresh tissue samples taken from the mesial structures of the temporal lobe amygdala and hippocampus were immediately frozen in liquid nitrogen. Catecholamines from amygdala and hippocampus were determined by high performance liquid chromatography (HPLC) with electrochemical detection, and amino acids were analyzed by HPLC with fluorescence detection.

RESULTS: Catecholamines and amino acids pathways were affected in patients with TLE in amygdala (A) and hippocampus (H). We observed an increase in noradrenaline in both regions compared to control patients. Serotonin was increased in A, but decreased in H. However, there was no significant change in the serotonin metabolite (5-HIAA) in A, and it was increased in H. Dopamine was also increased in both regions; in contrast, its metabolite (HVA) was decreased. Aspartate and glutamine showed a decrease, whereas glutamate levels were increased in the mesial structures of the limbic system. However, GABA concentration was increased in A and decreased in H.

CONCLUSIONS: These results show that catecholamines and amino acids pathways in the mesial structures of temporal lobe are involved in regulation of seizures in patients with intractable TLE. This imbalance in excitation and

inhibition may mediate some of the mechanisms involved in refractory epilepsy.

Sunday 4th July 2004
12:30 – 13:30

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VOLTAGE-GATED POTASSIUM CHANNELS IN FAMILIAL MESIAL TEMPORAL LOBE EPILEPSY

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PURPOSE: Voltage-gated potassium channels (VGKC) have been implicated in some types of idiopathic and symptomatic epilepsies. Recently, a type of autoimmune limbic encephalitis (LE) was associated with antibodies against VGKCs. In addition, patients with LE showed increased T2 signal abnormalities in limbic structures. We described a large group of families segregating familial mesial temporal lobe epilepsy (FMTLE) with evidence of a strong genetic predisposition to the development of hippocampal atrophy. The objective of this study was to carry out linkage analysis in FMTLE in order to investigate whether VGKC gene mutations may be present in these families.

METHODS: We studied two large kindreds with FMTLE (F-10 and F-26) with 57 individuals, including 32 patients. A total of 45 genes coding for VGKC were identified in different human chromosomes. We chose 83 polymorphic dinucleotide repeat markers, which flank all the VGKCs genes identified. The screening was performed by PCR amplification. Two-point lod scores (Z) were calculated for each family separately using the LINKAGE package.

RESULTS: To date, we have genotyped 47 markers, which excluded 21 VGKC candidate genes. The two Brazilian families segregating mesial TLE showed significant negative lod score for all markers genotyped, ranging from –2.43 to –7.66 at different recombination fractions.

CONCLUSIONS: Linkage studies are very efficient to identify disease related loci. By this method we can confirm or exclude genetic linkage between selected markers and disease loci. In the present study, we significantly excluded linkage between FMTLE and 21 genes coding for VGKCs.

6

FAMILIAL PERISYLVIAN POLYMICROGYRIA: CLINICAL FEATURES, GENETIC INVESTIGATION AND MRI FINDINGS

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PURPOSE: Congenital bilateral perisylvian syndrome (CBPS), which is most frequently caused by perisylvian polymicrogyria is characterized by epilepsy, pseudobulbar palsy and varying degrees of cognitive deficits. In some patients an association with chromosome 22q11.2 deletions and EMX2 mutations has been reported. The objective of this study is to describe patients with familial CBPS.

METHODS: We performed a clinical investigation of patients and their families. Patients were assessed by neuropsychological tests and language evaluation. In addition, all individuals included in the study had MRI scans. We analyzed the coding region of the EMX2 gene by the single-strand conformation polymorphism (SSCP) method in all patients.

RESULTS: We have identified 6 unrelated families with 12 patients with CBPS. Five patients had diffuse bilateral perisylvian polymicrogyria, 6 with bilateral posterior parietal polymicrogyria and 1 patient with bilateral fronto-parietal polymicrogyria. All patients had similar neurologic dysfunction, mainly primarily pseudobulbar paresis. Hemiparesis was present in only 1 patient. None of our patients had epilepsy. Specific language impairment was found in all individuals and global cognitive deficit was not present in most patients. Preliminary SSCP results did not show any abnormal band shift for EMX2 gene in our group of patients.

CONCLUSIONS: Severity of clinical manifestations in CBPS is correlated with the extent of cortical involvement. Epilepsy is not a common feature in familial CBPS. EMX2 gene seems not be involved in CBPS etiology in our cohort of patients. The 22q11 region may be a possible site for a gene influencing the development of the cerebral cortex and will be studied in our group of patients.

7

THE ROLE OF GABRA1 GENE AND THE 5Q34 CHROMOSOME REGION IN THE ETIOLOGY OF JUVENILE MYOCLONIC EPILEPSY

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PURPOSE: A missense mutation (Ala322Asp) in exon 9 of the GABRA1 gene, localized on chromosome (ch) 5q34, was found in a large French Canadian family segregating an autosomal dominant form of juvenile myoclonic epilepsy (JME).

METHODS: We performed mutation analysis of exon 9 of GABRA1 in 71 patients with IGE, 43 of whom with JME, and 82 normal controls. In addition, we carried out linkage and association analyses by genotyping four microsatellite markers flanking the GABRA1 gene on ch 5q34. Linkage studies were performed in six non-related families with all probands with JME. For the association studies we genotyped 43 non-related patients with JME and 63 normal controls.

RESULTS: We found only an intronic substitution, characterizing an common polymorphism in exon 9 of the GABRA1 gene (SNP rs = 2279020), which was present in patients and normal controls. Linkage analyses resulted in negative lod scores, excluding the entire 5q34 region. However, we found significant association between alleles of the two most telomeric markers genotyped on ch 5q34 (D5S422 and D5S2066) and JME.

CONCLUSIONS: We found that the mutation Ala322Asp in the GABRA1 gene is probably a rare event and does not represent a frequent cause of JME or other forms of IGE. We also excluded the presence of a major gene predisposing to JME and other forms of IGE on ch 5q34. However, this same chromosomal region may contain a gene of minor effect involved in the etiology of JME.

8

TIAGABINE SHOWS ANTICONVULSANT EFFECTS IN A FEBRILE SEIZURE MODEL IN RATS

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PURPOSE: The high incidence of epilepsy in the first decade of life and the propensity of children toward febrile seizures and status epilepticus are reflective of the increased susceptibility of the immature brain toward seizures. Numerous studies indicate that febrile seizures in early childhood may play an important role in the pathogenesis of temporal lobe epilepsy (TLE) and Ammon's horn sclerosis. Tiagabine (TGB) chemically, has a clearly defined mechanism of action and well-characterized pharmacodynamic and pharmacokinetic properties. The goals of the current study were to determine whether TGB administration prevents febrile seizures in infant rats.

METHODS: We used a hyperthermia-induced seizure model and assess the effects of TGB on the distribution of GAT-1 protein in the forebrain using an immunocytochemical method.

RESULTS: The results showed that TGB had different effects on seizures depending on the dose. Rats treated with TGB (15 mg/kg) 30 minutes prior to hyperthermia-induced seizures showed decreased number of seizures, decreased duration of seizures and increased latency to seizures as compared to untreated rats with hyperthermia-induced seizures. Both groups that received TGB showed sedation and ataxia as well as a loss in body weight as compared to the control group. Finally, both TGB treated groups showed a greater intensity of immunolabeled GAT-1 puncta throughout the hippocampal formation as compared to the control group.

CONCLUSIONS: These results show that tiagabine exerts an anticonvulsant effect in a febrile seizure model in rats. This effect may be mediated by increasing GAT-1 expression. These findings are consistent with increased GABA in the synaptic cleft that would trigger mechanisms for further enhancement of synaptic GABA levels.

Monday 5th July 2004
12:30 - 13:30

9

PATHOLOGICAL CHANGES IN THE TEMPORAL CORTEX, HIPPOCAMPUS AND AMYGDALA OF PATIENTS WITH INTRACTABLE TEMPORAL LOBE EPILEPSY (ITLE)

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INTRODUCTION: Epilepsy surgery is the treatment of choice in patients with ITLE as has been recently shown in a prospective meta-analysis comparing drug treatment versus surgery. Historically, a wide variety of morphological changes has been described.

PURPOSE: To define histopathological changes in the neocortex and mesial structures of the temporal lobe in surgically treated patients.

METHODS: Samples taken from 15 patients with ITLE submitted to surgery at the National Institute of Neurology and Neurosurgery were fixed, paraffin-embedded, stained with hematoxilin-eosin and Bielchowski and were morphologically analyzed.

RESULTS: Five cases were reported with an histopathological diagnosis of gliosis of the temporal neocortex showing central extensive chromatolisis, swelling and vacuolation of the cytoplasm, pyknosis and karyorrhexis of neurons. These samples also displayed highly condensed nuclei, and interstitial edema. Minor alterations were observed in hippocampus and amygdala. The remaining 10 cases showed only subtle pathological abnormalities in the neocortex and hippocampus, displaying a larger number of preserved neurons, as well as neuropil. However, 2 amygdala specimens presented extensive chromatolisis, pyknosis, swelling of the cytoplasm, highly condensed nuclei and karyorrhexis. The other 8 samples exhibited fewer morphological lesions.

CONCLUSIONS: The pathological changes observed in the surgical specimens of neocortex and mesial structures of the temporal lobe may be responsible for the lack of control of epilepsy with antiepileptic drugs (AED). The vast majority of changes observed are chronic in keeping with the longlasting nature of epilepsy. Probably some morphological changes may be induced by the chronic exposition and combination of AED's.

10

FEBRILE SEIZURES MODIFY THE TISSULAR CONTENT OF GABA, GLUTAMINE AND GLUTAMATE IN THE DEVELOPING RAT BRAIN

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PURPOSE: It has been described that immature brain is more susceptible to seizures than the mature brain and that febrile seizures early in life may lead to epilepsy. The goals of the current study were to determine the tissular content of GABA, glutamate and glutamine in some brain areas in infant rats using a hyperthermia-induced seizure model.

METHODS: 10 days old pups were placed on the floor of a 3l container and an air stream was directed ~50 cm above them. Hyperthermia was maintained for 30 min, aiming for a core temperature of 41° C. Thereafter, rats were placed on a cool surface, monitored for 15 min, and then returned to their home cages for rehydration by the mothers. The control group was under normothermic environment. Animals were sacrificed by decapitation 30 min, 24 h and 20 days after seizures and their brains were used for chromatography assay.

RESULTS: FS induced glutamine (1,636.2%) and glutamate (1,249.1%) increase in the cerebral cortex and GABA (310.2%), glutamine (206.2%) and glutamate (1,245.0%) in the amygdala and reduction in glutamine levels (68.6%) in the hippocampus 30 min after induced seizures as compared with the control group. However, 24 hours after the FS, the GABA (48.0%) and glutamate (64.3%) levels showed a reduction in cerebral cortex, and glutamine (44.5%) in hippocampus, whereas glutamate levels stay increased (667.0%) in the FS group. Twenty days after induced seizures, the GABA levels showed an increase (177.2%) in the cortex and amygdala (218.5%) as compared with the control group. The hippocampus showed an increased in glutamate levels (180.9%) as compared with the control group.

CONCLUSIONS: FS produced permanent changes in the tissular content of aminoacids in the immature rat brain. Moreover, it is possible that the enhanced inhibitory aminoacid levels 24 h and 20 d after FS may play a neuroprotector role to counteract the excess in glutamate levels.

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TREATMENT GAP: COMPARISON OF TWO PEDIATRIC EPILEPSY REFERRAL CENTERS IN CHILE AND COLOMBIA

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PURPOSE: To establish and to compare the treatment gap at the pediatric hospitals, Hospital Luis Calvo Mackenna in Santiago de Chile and Hospital Universitario San Vicente de Paúl in Medellín, Colombia.

METHODS: The variables of active epilepsy and appropriate treatment according to the ILAE Commission Report (2001) were established in pediatric patients with epilepsy assisting to the two hospitals during a four months period. The treatment gap was expressed in percentages and its possible causes were searched using a questionnaire.

RESULTS: A total of 228 patients were examined; 99 (43.4%) in Chile and 129 (56.6%) in Colombia. Of those, 162 (71%) had active epilepsy; 71 (71.7%) in Chile and 91 (70.5%) in Colombia. The number of patients with epilepsy and appropriate treatment was 129; 61 (85.9%) in Santiago and 68 (74.7%) in Medellín. The global treatment gap was 20.4%; 14.1% in Santiago and 25.3% in Medellín. The main factors for the treatment gap in Colombia were the erroneous medical antiepileptic drug prescription (52%), followed by the patient's poor adherence to medical instructions (34.7%). The main reasons for the treatment gap in Santiago were the economic burden to buy the antiepileptic drugs (50%) followed by the patients' irregular adherence (30%).

CONCLUSIONS: Considering the high treatment gap percentages, the following recommendations are suggested: 1. Medical training in epilepsy should be reinforced, emphasizing pharmacologic treatment and prescription. 2. Education and information programs for patients aimed to warrant patients' pharmacologic compliance should be encouraged. 3. Social security systems and governmental programs on epilepsy should strongly consider and cover the economic burden of epilepsy in Latin America.

12

KETOGENIC DIET AND REFRACTORY EPILEPSY: A CHILEAN SERIES

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PURPOSE: Determine safety, efficacy and compliance with the Ketogenic diet (KD) in patients with refractory epilepsies.

METHODS: We prospectively studied 27 patients (12 male; aged 8 months to 20 years-old), with diagnosis of refractory epilepsy, hospitalized and followed-up at the Neurology Unit of a public hospital, that provides care for low income population. Mean evolution time since diagnosis was 4.5 years (6 months-20 years). Epilepsy types: Generalized cryptogenic (n = 2), West Syndrome (n = 4), Lennox Gastaut (n = 3), Myoclonic Epilepsies (n = 8), Focal Symptomatic (n = 9) and Otahara Syndrome (n = 1). Inclusion criteria: No seizure control after 6 months of polytherapy, significant side effects or adverse reactions to several antiepileptic drugs (AED), caregivers able to understand how to prepare and administer the KD and patients aged over 6 months. Patients received a high-fat, very-low carbohydrate diet (4/1 proportion) according to Johns Hopkin Hospital protocol. Response was defined as > 70% of seizure reduction.

RESULTS: Mean follow-up was 21 months (1-72 months). 19/27 cases (70.3%) responded favorably: between 25% response in West Syndrome and 100% in Lennox Gastaut. Five patients became seizure free (18.5%). Thirteen patients (48%) were withdrew from the KD: 10/27 due to perceived restrictiveness or refusal to receive it and 3/27 due to complications. Adverse side effects included: hypoproteinemia (1), hydroelectrolytic imbalance (1), hematuria (1), nephritis (1), kidney stones (1), fecaloma (1).

CONCLUSIONS: KD is a safe, well-tolerated and effective alternative treatment in most patients with refractory epilepsy. All types of epilepsies may improve. The number and doses of AED were reduced in responding patients and their quality of life was improved. This experience, obtained in a non-developed country, is comparable to European and American series.