Phenotypic characterization and preliminary genetic studies of a large cohort of patients with childhood epileptic encephalopathy (CEE).

HT Moraes[1], MC Gonsales[1], L Sauma[2], CV Soler[1], PAO Ribeiro[1], ML Santos[1], MM Guerreiro[2], MA Montenegro[2], AC Coan[2], BS Carvalho[3], I Lopes-Cendes[1]

[1]Department of Medical Genetics, [2]Department of Neurology; School of Medical Sciences; [3]Department of Statistics, Institute of Mathematics, Statistics and Computer Science; University of Campinas, UNICAMP, Campinas, SP, BRAZIL and the Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, SP, BRAZIL.

Introduction: CEEs is a heterogeneous group of rare and severe epilepsies characterized by different types of seizures with difficult control and high-risk of progressive neurological deterioration [1]. There are different clinical types of CEEs related with the age of onset including: Dravet syndrome, Doose syndrome, Ohtahara syndrome, early myoclonic encephalopathy, West syndrome, Lennox-Gastaut syndrome, epilepsy of infancy with migrating focal seizures, epileptic encephalopathy with continuous Spike-and-wave during sleep and Landau-Kleffner syndrome [2]. The diagnosis of CEE is based on clinical data and electroencephalogram results and the etiology remains unknown in most patients. Even with the progress of molecular studies and the identification of new mutations associated with CEE a significant number of the patients still do not have a major genetic variant identified, since only 1-2% of epilepsies are considered monogenic [3]. This highlights the need for additional studies using complex models of genetic inheritance. Therefore, the main objective of this study is to access a large cohort of patients and to characterize them in detail from the phenotypic and genetic aspects, including search for genetic variants which may cause CEE in a single gene or polygenic inheritance. In preparation for our genetic studies we describe here the results of the detailed clinical characterization of these patients as well as some preliminary genetic results.

Materials and Methods: All patients with CEE diagnosis followed at our childhood epilepsy clinic from the year 2000 to today were invited to participate in this study. In addition, we received samples for the genetic study of patients from different centers in Brazil. Clinical data was collected following a standard protocol by the treating physicians. To date, we have accessed a total of 171 patients with different CEE syndromes. One hundred and thirty-three of whom have been tested for the presence of mutations in six candidate genes using Sanger sequencing and a next-generation sequencing panel. The results of the sequencing experiments were analyzed using different bioinformatics algorithms and compared to a panel of 200 normal individuals of the Brazilian population, data available at www.bipmed.org.

Results: Of the 171 patients, 99 were male (57.9%) and 72 were female (42.1%). We obtained the birth date on 99 patients and age of onset of seizures on 99 different patients and determined that the current age ranged from 1 to 42 years old (mean 12.7 years) and the age of onset of seizures ranged from 0 (within the first month of life) to 132 months (mean 23.8 months). We also obtained DNA samples from 151 patients and tested 133 for the presence of mutations. Preliminary genetic studies showed 19 patients with mutations in the *SCN1A* gene (14.2%), one patient with a mutation in the *SCN2A* gene (0.7%), ten patients with mutations in the *SCN1B* gene –(7.5%) and, most interesting, five patients with mutations in both *SCN1A* and *SCN1B* genes (3.8%).

Discussion: Assuming a monogenic inheritance we were able to make the diagnosis in only 26.2% of 133 patients with CEE. We believe that as our project progresses and we add new bioinformatics analysis, especially considering a polygenic inheritance, we will increase the yield of molecular diagnosis.

Conclusions: We report preliminary results of clinical and genetic characterization of a large cohort of patients with CEE. To our knowledge, this is the largest study of this kind in Latin America and it is likely to significantly contribute to a better understanding and diagnosis of CEEs. We also aim to make public at www.bipmed.org all genetic data acquired in this study, contributing further to improve research in this field.

References: [1] doi: 10.1016/S1474-4422(15)00250-1; [2] doi: 10.1590/0004-282X20150122; [3] doi: 10.1111/j.1469-8749.2008.03058.x.