Clinical features and gene mutational spectrum of CDKL5-related diseases in a cohort of Chinese patients.
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This study from Peeking University is the first detailed report from China on children with a CDKL5 disorder. Some of the authors were involved in a previous report that included a male with a CDKL5 mutation but no specific details were included then. In this study, 102 individuals who had a diagnosis of either early-onset epileptic encephalopathy or of Rett syndrome were screened for a CDKL5 mutation. There were 71 female and 31 males whose ages ranged from 1 month to 12 years (average 16 months). There were 64 who presented with early onset epileptic encephalopathy (36 with infantile spasms, 8 with Ohtahara syndrome and 20 with an unknown epileptic syndrome), while 38 had a diagnosis of Rett syndrome (16 classical, 10 congenital, 3 preserved speech variant and 9 Hanefeld variety). All of those with early onset epileptic encephalopathy had developed seizures within 6 months of age while none of those with a diagnosis of Rett syndrome had a MeCP2 mutation.

Mutations were identified in 10 (9.8%) of the 102 who were screened. There were 9 females and 1 male. Of the 9 females, 7 were from the 9 with the Hanefeld variant while the other 2 had previously been diagnosed with an unknown epileptic syndrome. The 1 male identified had infantile spasms. As noCDKL5 mutations were found in parents these were all considered de novo mutations. A variety of mutation types were seen with 5 occurring in that part of the gene coding for the kinase domain while the other 5 affected the C-terminal. Patterns of X-inactivation were fairly random with a range from 50:50 to 63:37.

All affected individuals developed seizures by 4 months of age, and various seizure types presented during the course of their development, including epileptic spasms, partial seizures, myoclonic seizures and tonic seizures. All types of seizure were said to be intractable and resistant to antiepileptic drugs - although 1 patient with a splice mutation affecting the kinase domain was said to be seizure free from 3 years of age.
EEG studies revealed a hypsarrhythmia in 5 patients. Some Rett-like features had developed in the 9 female patients, such as hand-mouthing, hand washing or clapping. All individuals showed severe psychomotor developmental delay. In addition, hypotonia, poor to absent acquisition of language, limited hand skills, poor eye contact, features of autonomic dysfunction and autistic symptoms were present. There was 1 child who had taken a few steps by the age of 6 months and another who had apparently spoken one word. The male patient in the study is relatively young and his development is still being monitored. MRI, blood and urine amino acid and organic acid investigations were all normal.

Note - a nice paper and reasonably comprehensive review of 10 patients that endorses the features we all now recognise. It is interesting that none of those patients who had initially been diagnosed with the classical, congenital or preserved speech variant form of Rett were found to carry a CDKL5 mutation - and none of them had a MeCP2 mutation either. It is not apparent whether mutations affecting other genes - eg FOXG1 - were sought. Conversely, 7 of the 9 with the Hanefeld variant had a CDKL5 mutation. In 1985, Hanefeld described cases of infantile spasms in patients who later developed many characteristics of Rett syndrome - and so he ultimately may have been the first to have reported individuals with a CDKL5 disorder.