

# Epileptic encephalopathy and atypical Rett syndrome with mutations in CDKL5: clinical and molecular characterization of two Brazilian patients

Encefalopatia epilética e síndrome de Rett atípica por mutações no gene CDKL5: caracterização clínica e molecular de dois casos brasileiros

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Mutations in the CDKL5 gene cause early onset epilepsy, infantile spasms with hypsarrhythmia on the electroencephalogram (EEG) and atypical Rett syndrome. Axial hypotonia, severe developmental delay and autistic spectrum disorder are also frequently found in patients with these mutations<sup>1</sup>.

Different epileptic manifestations were described in patients with mutations in the CDKL5 gene, including seizures with onset at the first six months of life, infantile spasms and myoclonic epilepsy<sup>1,2</sup>.

In 2007, the two first Brazilian patients with Rett syndrome and mutations in the MeCP2 gene were reported<sup>3</sup>. Here, we described the clinical condition and characterization of the two first Brazilian patients with CDKL5 mutations, including the first Brazilian case of atypical Rett related to abnormalities in this gene.

Both girls presented severe developmental delay, axial hypotonia, early onset seizures highly resistant to treatment and hypsarrhythmia. Case 2 also presented a Rett-like phenotype. A small mutation in one allele of exon 8 of the CDKL5 gene, c.549dupA, was found in Case 1, and, in Case 2, a mutation in the Xp22.3 locus detected by array-CGH deleted the whole CDKL5 gene in one allele.

In Case 1, an apparently normal development was reported until the age of two months, when the patient was affected by clonic partial evolving to generalized seizures. Case 2, like most cases related to abnormalities in this gene, presented developmental impairment and hypotonia described to be noticed since the first days of life, although the seizures onset

occurred later compared to the average rate previously described, at six months<sup>1,4</sup>.

We observed in our patients the three-step epilepsy phenotype recently associated with CDKL5 mutations, both presenting refractory epilepsy with multifocal activity on the EEG, described to be associated to a more severe phenotype. A group of patients with a better outcome was also reported in the literature. In those, "honey-moon" periods, after anticonvulsants introduction, became permanent with complete absence of seizures, even though neurological condition and hypotonia



**Figure.** Patient 2, at three years and six months, presenting elongated skull and prominent ears. Array-CGH showed a 1,6Mb "de novo" deletion at Xp22.13, which included the whole CDKL5 and NHS genes in one allele.

remained stable<sup>4</sup>. In Case 1, progression to the late stages occurred despite the decrease in seizures frequency, at one year and eight months, with subsequent improvement of neurological condition.

No unique EEG pattern is observed in patients presenting CDKL5 mutations. Interictal EEG is usually normal at epilepsy onset, or shows background slowing, however focal and multifocal discharges were also previously described<sup>4</sup>. Posteriorly, a progressive deterioration with slowing of basal rhythm and disappearance of physiological features tend to occur, with subsequent development of epileptic encephalopathy<sup>4</sup>. In Case 1, the first EEG detected, besides background slowing,

interictal activity in left temporal lobe, and, in Case 2, diffuse abnormalities in a normal background.

In Case 2 (Figure), the presence of Rett-like features, such as stereotypies, hyperventilation, bruxism and hand apraxia, in the absence of an early normal period due to the presence of seizures, is consistent with atypical Rett caused by CDKL5 mutations<sup>5</sup>.

This study reinforces the previously reported phenotype related to mutations in the CDKL5 gene. Epilepsy with onset within six months of life, especially in the presence of infantile spasms, in females with psychomotor impairment in the first months and hypotonia, strongly suggests screening for mutations in this gene.

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