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Brain & Development 31 (2009) 469–472

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case report

Expansion of the first polyalanine tract of the *ARX* gene in a boy presenting with generalized dystonia in the absence of infantile spasms

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Received 11 April 2008; received in revised form 8 August 2008; accepted 8 August 2008

Abstract

Mutations in the Aristaless-related homeobox (*ARX*) gene are associated with pleiotropic phenotypes including infantile spasms, mental retardation and dystonia. However, relatively consistent genotype–phenotype correlations have been emphasized in prior reports. We report a boy presenting with mental retardation, tonic seizures and dystonia but without infantile spasms. Gene sequencing detected an additional seven GCG repeats in the first polyalanine tract of the *ARX* gene, a mutation which leads to an expansion of the normal 16 alanine residues to 23. The same *ARX* gene mutation has been reported in patients with infantile spasms, but was absent in the present case. This finding highlights the diverse phenotypic spectrum that may result from *ARX* gene mutations.

Keywords: *ARX* gene; Mental retardation; Infantile spasms; Dystonia

1. Introduction

The Aristaless-related homeobox (*ARX*) gene is located at Xp22 [1]. *ARX* is considered to have an important role in neuronal proliferation, interneuronal migration and differentiation in the embryonic brain, and also in the differentiation of Leydig cells of the testis [2]. Expression of the *ARX* gene was detected in the brain, and mutations were identified in families with mental retardation, epilepsy, and dystonia by Stromme et al. in 2002 [1].

Since the identification of the *ARX* gene, diverse clinical cases featuring mutations have been reported. *ARX* mutations show marked pleiotropy in the phenotype they produce, but consistent genotype–phenotype correlations have been reported [3].

Herein we report a case with seven additional GCG repeats in the first polyalanine tract of *ARX*, which is known to be associated with infantile spasms. Our patient had mental retardation, dystonia and tonic seizures but no infantile spasms, a phenotype distinct from previously reported cases with the same mutation.

2. Case report

This five-year-old boy was the first and only child of unrelated healthy parents. Family history was non-con-

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doi:10.1016/j.braindev.2008.08.006

tributory. He was delivered by cesarean section at 41 weeks gestational age without complications. His birth weight (3860 g), height (51 cm), and head circumference (35.5 cm) were all within ±2 standard deviations of age-appropriate norms. At the age of 4 months, his parents noticed his right upper limb would periodically extend and internally rotate, and dystonia was diagnosed at 7 months. Developmental milestones were delayed, and he lacked head control. Physical examination, including testes exam, was unremarkable. Findings from blood, cerebrospinal fluid and urine examinations at 8 months were normal. MRI of the brain showed mild brain atrophy and cavum septum pellucidum. Single photon emission computed tomography revealed hypoperfusion in the left caudate nucleus and bilateral thalami. EEG was normal.

When he was 1 year 6 months old, he had a generalized tonic–clonic seizure associated with fever. At 3 years 7 months old, he suffered a tonic seizure without fever, accompanied by cyanosis, and interictal EEG showed spikes over the bilateral frontal areas. He was diagnosed with frontal lobe epilepsy and was treated with phenobarbital and zonisamide. This regimen was effective, but his seizure recurred at 4 years 2 months, and he developed apneic fits. At 4 years 7 months, nocturnal myoclonus became markedly worse.

Clinical examination at 5 years 8 months was significant for severe psychomotor delay. He could not sit or crawl and had no words. He showed paroxysmal generalized dystonia, with the right arm extended and internally rotated, left lateral neck rotation, and opisthotonic posturing. Deep tendon reflexes were normal. Brain MRI findings were unchanged (Fig. 1), and the interictal EEG showed frequent paroxysmal parietal discharges (Fig. 2). He had tonic seizures lasting for 1–2 min at least once a week.

Given the constellation of clinical findings, including severe psychomotor delay, epilepsy and dystonia, an *ARX* gene mutation was suspected. Accordingly, *ARX* gene sequencing was performed after informed consent was obtained from his parents. Genomic DNA from a peripheral blood sample was extracted according to standard procedures. Each exon of the *ARX* gene was amplified by PCR using primers designed to amplify coding and flanking non-coding regions of the gene (GenBank # AY038071.1). Bidirectional cycle sequencing reactions were performed with the ABI Big Dye Terminator Sequencing Kit (Applied Biosystems) and the purified products were subject to an automated capillary array sequencer (ABI 3100, Applied Biosystems). Sequencing results revealed an insertion of seven GCG repeats in the first polyalanine tract in exon 2 of the *ARX* gene. The normal 16 alanine residues were thus amplified to 23 alanine residues by this mutation.

3. Discussion

The patient exhibited generalized dystonia from 4 months of age. He also had profound psychomotor delay, and developed generalized tonic–clonic seizures at 1 year 6 months. Neurological disorders associated with dystonia, such as cerebral palsy due to neonatal asphyxia, glutaric aciduria type I, and dentatorubral-pallidoluysian atrophy were initially suspected, but were ruled out by his clinical course and available laboratory and imaging data. Although the absence of infantile spasms or abnormality of the corpus callosum made us discount the possibility of an *ARX* mutation at first, his persistent generalized dystonia finally led us to this diagnosis.

Phenotypes associated with *ARX* mutations include both brain malformation and non-malformation syndromes [3]. There is a good correlation between genotype and phenotype in most *ARX* mutations. Premature termination mutations and missense mutations in the homeobox domain cause malformation syn-

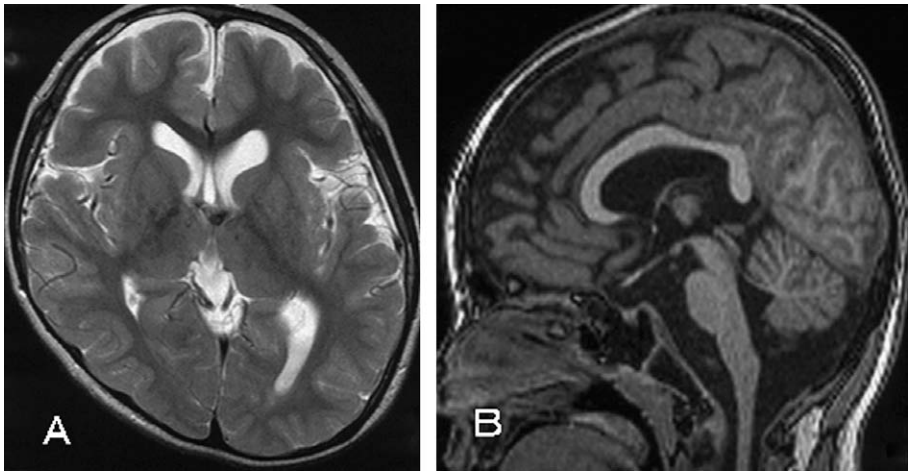

Fig. 1. Brain MRI at 5 years 8 months. (A) Axial T2 weighted image demonstrates mild brain atrophy and cavum septum pellucidum. (B) Sagittal T1 weighted image demonstrates normal structure of the corpus callosum.