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Dystonia in a Patient With Ring Chromosome 21

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Abstract: Dystonia associated with chromosomal abnormalities is typically attributed to chromosomal deletions. We describe a patient with ring chromosome 21, with karyotype 46XX,r(21)(p11.2q22.3); 46,XX,dic r(21)(p11.2q22.3); 45, XX, –21, who developed childhood onset cervical dystonia. © 2003 Movement Disorder Society

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Childhood onset dystonia is a heterogeneous disorder that occurs due to a variety of etiologies. Mutations in the DYT-1 gene account for a large percentage of childhood-onset generalized dystonias.¹ Other less common monogenetic dystonias include dopa-responsive dystonia (DYT5)² and myoclonus-dystonia (DYT11).³ A set of dystonia-plus syndromes (DYT 8, 9, 10) present as paroxysmal dystonia with episodes of involuntary movement in infancy or childhood.^{4–6} In addition, childhood-onset dystonia may result from congenital malformations^{7,8}; inborn metabolic disorders such as glutaric aciduria,⁹ Leigh's disease,¹⁰ homocystinuria,¹¹ kernicterus, gangliosidosis^{12,13}; and infectious diseases such as mycoplasma.¹⁴ Cervical spine trauma due to delivery, ectopia lentis, and trochlear palsy may masquerade as cervical dystonia.^{15–17}

A videotape accompanies this article.

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The ring chromosome is a rare chromosomal abnormality resulting from the breakage and reunion of both chromosome arms. The phenotype of a ring chromosome depends upon the genetic sequences deleted or duplicated. Trisomic and monosomic presentations have been described with ring chromosome 21.^{18,19} Phenotypes associated with ring chromosome 21 have ranged from a normal, intelligent female to individuals with severe craniofacial dysmorphisms, congenital heart defects, and growth and motor retardation.²⁰ However, most individuals with ring chromosome 21 demonstrate a non-uniform pattern of down-slanting palpebral fissures, deep-set eyes, small mandible, low-set ears, genital hypoplasia, growth retardation, and mild-to-moderate mental retardation.^{6,20}

This report, documenting a second individual with torticollis and ring chromosome^{21,21} provides supportive evidence for a possible role of the 21q22 locus in the pathogenesis of cervical dystonia.

Case Report

The patient's mother provided written informed consent for publication of this case report and this report was approved by the Washington University School of Medicine Human Studies Committee.

The patient was born at 35 weeks gestation by ultrasound to a 31-year-old gravida 4, para 3 mother via an uncomplicated vaginal delivery. A prenatal ultrasound at 5 months gestation was normal. The pregnancy was notable for first trimester spotting and midgestation urinary tract infection. Screening for group B *Streptococcus* antigen at birth was negative. Examination at birth revealed low-set ears, facial and hand dysmorphisms, and a heart murmur. She did well in the immediate neonatal period without need for intervention. At 6 months her family observed that her head tilted to the right and attempts to straighten her neck seemed to cause pain. Head position was improved when lying down. There was no clear sensory trick. She had two focal seizures with secondary generalization at ages 2 and 4 years that were treated with phenobarbital. She stood with assistance at 20 months. Currently, at the age of 6 years, she walks with a walker. She spoke her first words at 12 months of age. She can put two to three words together with about fifty percent intelligibility.

At age 6 years old, she was evaluated for cervical dystonia. On initial examination, she was alert and produced few intelligible words. She had a head circumference of 102 cm (5% percentile) and weight 16 kg (5% percentile) based upon standard growth curves. She had downwardly slanted eyes and low set ears. Ophthalmologic examination revealed no oculomotor abnormalities. She had cervical dystonia characterized as moderate torticollis, severe laterocollis, and mild retrocollis. The modified Tsui dystonia rating scale score was 16.^{22,23} There was moderate spasm of the right trapezius, levator scapulae, and sternocleidomastoid but only mild spasm on the left side of her neck. She had four-limb spasticity, slightly more prominent on the left. Deep tendon reflexes were brisk and plantar reflexes were extensor.

Chromosome analysis of peripheral blood cells at age 1 week demonstrated a mosaic pattern that consisted predominantly of a ring chromosome 21. The majority of cells (86%) were equally split between 46,XX,r(21)(p11.2q22.3) and 46,XX,dic r(21)(p11.2q22.3) resulting in a deletion of terminal bands of the short and long arms of chromosome 21. A small number of cells (14%) had monosomy 21 (45,XX,-21). Parental karyo-

types were normal. A head computed tomography (CT) at age 2 years showed periventricular calcification. Brain magnetic resonance imaging (MRI) demonstrated mild periventricular leukomalacia and a few punctate periventricular calcifications. No heterotopic gray matter areas were seen. A complete blood count and metabolic panel were normal. Cervical spine radiographs revealed congenital fusion of C2 and C3 vertebral posterior elements.

We treated her cervical dystonia with 60 units (3.8 U/kg) of botulinum toxin A (Botox; Allergan, Irvine, CA). She received splenius 10 units \times 2, levator scapulae 10 units \times 2, and sternocleidomastoid 10 units \times 2. The patient experienced improvement of head positioning and attention to tasks after botulinum toxin injections lasting 8 months. She had no side effects. Repeat injections provided comparable benefit.

Discussion

This report represents the second case of dystonia associated with ring chromosome 21. In this case, common secondary etiologies and causes of abnormal head position without dystonia, fourth nerve palsy, and atlantoaxial dislocation were carefully excluded. The improved range of motion to the midline after botulinum toxin injections excludes bony fusion as the cause of her torti- and laterocollis. Although she was born prematurely at 35 weeks, there was no suspected fetal distress or hypoxia. Two brain MRI studies showed no pathology in the basal ganglia. The relationship between periventricular leukomalacia and her focal dystonia is less clear. Periventricular leukomalacia is a common radiologic finding in infants born prematurely and is thought to result primarily from ischemic injury to oligodendroglial precursor cells during a susceptible period in the third trimester of gestation.²⁴ Our patient's periventricular leukomalacia was likely a consequence of prematurity. The periventricular calcifications are suspicious for TORCH infection in the perinatal period and such infection cannot be excluded. No basal ganglia damage was seen on MRI, however, and the dystonia was highly focal. Given the focal nature of her dystonia, the onset at age 6 months, and exclusion of other common causes of dystonia, we feel that her dystonia is most likely due to the chromosomal abnormality.

Three separate mechanisms have been described in familial and sporadic cases of ring chromosome 21.¹⁸ First, ring chromosomes can result from breakage in both chromosome arms and fusion of the breakpoints. Second, an intermediate isochromosome or Robertsonian translocation chromosome may undergo asymmetric breakage and reunion of the long arms. This leads to a dicentric ring chromosome with duplication of a single copy of the proximal portions of the long arm. Third, two ring sister chromatids formed by the first mechanism may exchange genetic material resulting in a mosaic karyotype with various sized rings. In our patient, the single centromeric ring chromosome and uniformly sized dicentric rings suggest the first two mechanisms were present. All mechanisms of ring chromosome formation result in deletion of genetic material distal to the breakpoints. Therefore, the expected phenotype of this case would be that of deletion of genes distal to chromosome 21 loci p11.2 and q22.3.

A previous report describes a patient with an atypical Down syndrome phenotype and torticollis at age 5 weeks.²¹ The karyotype was a mosaic of translocation trisomy 21 and ring chromosome 21. The breakpoint for the ring chromosome was at 21q22. The affected cell lines were trisomic for genes be-

tween the centromere and loci q22, but monosomic for the terminal portion distal to loci q22. Our patient had a deletion in the same region and the predominant phenotype in our patient was deletion of chromosome 21q. Therefore, it is possible that the loss of genetic material terminal to loci q22.3 is responsible for dystonia. Genes in this region include cystathionine beta-synthase,²⁵ EPM1,²⁶ DCR,²⁷ and alobar holoprosencephaly-1 (HPE1).²⁸ Further study of these genes in genetic and sporadic dystonia syndromes may be warranted.

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Legend to the Video

Brief video of the patient demonstrating severe latero- and torticollis. This video was taken before treatment with botulinum toxin A injections.

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