Adult-Onset Dystonia in Aicardi-Goutières Syndrome

Aicardi-Goutières syndrome (AGS) is a rare, genetically determined encephalopathy with features mimicking congenital infection (microcephaly, bilateral basal ganglia calcifications, cerebral white matter abnormalities, cerebral atrophy, chronic CSF lymphocytosis, and elevated CSF INF-α). Disease onset usually occurs during the first year of life as a subacute encephalopathy and then the clinical picture appears to stabilize with no further disease progression. Typically, patients are left with limb spasticity, dystonic posturing, and truncal hypotonia, with almost all patients severely intellectually and physically impaired. We report the investigational work-up of an adult-onset dystonia in a patient previously diagnosed with cerebral palsy.

A 26-year-old woman with a previous diagnosis of cerebral palsy was referred to botulin toxin treatment. She was the third child of healthy unrelated parents, born full term. The description was of normal psychomotor development until 7 months of age, when subacute illness developed with regression of the majority of milestones. She developed spastic diplegia and completed the ninth grade in regular school at the age of 19. At the age of 24, she noted progressive abnormal posturing of the neck, trunk, and upper limbs. She had two sisters, one of them described as having a severe form of cerebral palsy. Neurological examination revealed a slight mental delay, generalized dystonia with involvement of the face (perioral), neck (retrocollis with left chin deviation), trunk and limbs, with particular involvement of the left upper limb, spastic tetraparesis, predominantly of the lower limbs, with brisk reflexes and flexor plantar response (Fig. 1; Video). Head circumference was normal. There were chilblain lesions on her toes. An MRI, extensive laboratory investigation, and genetics of mitochondrial cytopathies were normal or negative. Observing the family, one sister was normal and the other, a 29-year-old woman, presented profound psychomotor delay, intermittent eye contact with no language, severe generalized dystonia and pyramidal tract signs (Video). Chilblain lesions were also identified. She was abnormal since birth and never acquired any psychomotor milestones. A cerebral CT scan revealed multiple spontaneous hyperdense foci in the putamina suggestive of TORCH complex congenital infection (Fig. 1). Given the family history and the bilateral basal ganglia calcifications, AGS was considered. Genetic testing detected the AGS2/RNASEH2b mutation c.529G>A, p.A177T, in exon 7 in a homozygous
state confirming the clinical diagnosis of AGS. A CT scan performed on the index case revealed brain calcifications in a similar pattern but with minor extension (Fig. 1). A CT scan performed to the unaffected sister was normal.

AGS is usually a pediatric diagnosis and not regularly seen or considered in adult clinical neurology. The clue for considering the diagnosis was the calcifications found in the CT scan of the patient’s sister. Intracranial calcifications are not always detected in MRI. Consequently, when considering AGS in the differential diagnosis, CT should be performed or attempts should be made to add a T2* sequence or susceptibility weighted imaging to the MRI protocol to increase sensitivity. At the first clinical observation, despite the presence of the cutaneous lesions, we did not consider them as part of the clinical syndrome. Chilblains are present in over 40% of mutation-positive individuals and seem to be a highly specific diagnostic sign. CSF analysis was not performed because the level of white cells and INF-α of AGS-affected patients usually falls to normal over the first few years of life. On the basis of the retrospective assessment, it seems that the less affected sister has a later-onset form and the older sister has a probable neonatal form of the disease. RNASEH2B mutations are associated with a significantly later age at presentation and lower childhood mortality. Our patients remained alive at the ages of 30 and 28 and the index case presented only slight mental delay with moderate learning difficulties, confirming this genotype-phenotype association. The different severity of clinical expression in these siblings also confirmed the phenotypic heterogeneity of the disease even in the same sibship. To our knowledge, this is the first description of a late-onset dystonia in AGS, expanding the clinical phenotype of the syndrome.

Our case highlights the importance of recognizing AGS in the differential diagnosis of adult movement disorders that fall under the cerebral palsy umbrella. Brain calcifications and chilblains are particularly valuable in pointing to the diagnosis in adult patients.

Legends to the Video

Segment 1. Index case at the age of 6, 8, and 24 years old. It shows no neck, trunk, or upper limbs dystonia in childhood. At 24 years old, a slight abnormal posture of the neck was present.

Segment 2. Index case, at the age of 26, handling a paper, at rest, with arms in extension and in alar posture. The dystonia worsened with movement and alar posture, developing a severe dystonia affecting face (perioral), neck (retrocollis with left chin deviation), trunk and upper limbs, with particular involvement of the left arm.

Segment 3. Index case after botulinum toxin treatment with improvement of dystonia. Finger nose testing is normal.

Segment 4. The affected sister of the index case observed in bed. There are oromandibular dystonia with jaw open and sometimes movements of tongue protusion, retrocollis is very exuberant and axial dystonia is particularly severe with permanent sciotic posture. The limbs are also involved. All the observed movements are pointless. Myoclonic jerks were also present.

Segment 5. Chilblain lesions in left hand and feet of the affected sister of the index case.

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References