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Clinical Observations

Early Diagnosis of CAPOS Syndrome Before Acute-Onset Ataxia—Review of the Literature and a New Family

Anna Duat Rodriguez MD, PhD [a,*], Michaela Prochazkova MD [a], Saturnino Santos Santos MD [b], Oscar Rubio Cabezas MD, PhD [c], Veronica Cantarin Extremera MD [a], Luis Gonzalez-Gutierrez-Solana MD [a]

[a] *Department of Pediatric Neurology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain*
[b] *Ear, Nose and Throat Department, Hospital Infantil Universitario Niño Jesús, Madrid, Spain*
[c] *Department of Clinical Genetics, Hospital Infantil Universitario Niño Jesús, Madrid, Spain*

ABSTRACT

BACKGROUND: CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss) is a rare disease that has been reported in 22 patients so far. In all cases, the mutation c.2452G>A (p.Glu818Lys) in the *ATP1A3* gene was identified. Patients typically present at an early age with an acute-onset fever-induced episode of ataxia frequently associated with encephalopathy and weakness. They usually present one to three episodes. The acute symptoms improve within days, but most patients show slow progression afterward. **METHODS:** We describe three new patients, a woman and her two sons diagnosed with CAPOS syndrome. A systematic review of literature on previously reported patients was performed. **RESULTS:** The first son presented with acute-onset ataxia, encephalopathy, and sensorineural hearing loss, induced by febrile illness. The second one developed generalized areflexia and mild instability without an acute episode. The mother had been previously diagnosed with sensorineural hearing loss and optic nerve atrophy. The c.2452G>A mutation in *ATP1A3* was found in all three patients. **CONCLUSION:** Only 25 Individuals with CAPOS syndrome have been reported, including our family. This is the first time a Spanish family has been described. The fact that both siblings were assessed before the first acute-onset episode contributes to the description of early symptoms and signs of the disease, which could aid early diagnosis and management before the onset of acute episodes.

Keywords: CAPOS syndrome, *ATP1A3* gene, cerebellar ataxia, sensorineural hearing loss, optic atrophy

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Introduction

CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss) was first described 20 years ago,[1] but it was not until 2014 that the pathogenic mutation c.2452G>A (p.Glu818Lys) in *ATP1A3* gene was identified.[2] Since then, 22 patients have been reported.

Patients typically present at an early age with an acute-onset fever-induced episode of ataxia frequently associated with encephalopathy and weakness. Recovery from the episode is usually complete; occasionally, mild sequels can be observed. Afterward, the patients show a slow progression of the disease.

Although the acute episodes have been well described in all documented patients, only one patient underwent a neurological examination before the acute onset of the disease.[3]

This article reviews the literature and describes a mother and her two sons with CAPOS syndrome. The mutation c.2452G>A (p.Glu818Lys) in the *ATP1A3* gene was identified in all three affected family members. Both children had been assessed in our neurology department before their first acute episode.

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* Communications should be addressed to: Dr. Duat Rodriguez; Hospital Infantil Universitario Niño Jesús; Avenida Menendez Pelayo 65; Madrid 28009, Spain.
E-mail address: annaduatr@gmail.com

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Patient Descriptions

Patient 1

This now an eight-year-old boy was assessed for the first time for mild motor development delay at age three years. His parents had observed clumsiness and poor coordination since he started to walk independently at age 15 months. His medical history was uneventful. His neurological examination revealed a slight motor impairment, with frequent stumbling and areflexia in the legs. Electromyography and peripheral nerve conduction study were normal. Eye examination, including funduscopy, audiometry, and brainstem auditory evoked potentials, which were performed because of his mother's sensorineural hearing loss and optic atrophy, were normal.

Six months later, during a febrile influenza A infection, he was hospitalized with intense malaise and anorexia. He progressively developed ataxic gait and altered mental status. Encephalitis was suspected and intravenous acyclovir was started. Brain imaging, laboratory testing, and lumbar puncture were unremarkable (Table 1). The encephalopathy and gait disturbance improved within a few days, but a severe bilateral sensorineural hearing loss was observed. Although there were no clinical signs of visual loss, an eye examination revealed pale optic discs. None of these findings were present at the initial assessment 6 months earlier.

The clinical signs suggested hereditary mitochondrial disease: acquired sensorineural hearing loss, areflexia, optic nerve atrophy, and mild ataxia. Because the family refused a muscle biopsy and the patient's mother also had sensorineural hearing loss and optic nerve atrophy, she underwent a muscle biopsy. Histopathological examination of the muscle, respiratory chain enzymes studies, and genetic testing of point mutations in a panel of mitochondrial genes were normal. Genetic testing for mitochondrial disorders, *OPA-1* gene, and spinocerebellar ataxias (Table 1) was performed in the patient, and he was started on carnitine.

Since then, the patient has not experienced additional acute episodes. The hearing loss and mild ataxia, which he developed after the first episode, has remained unchanged over years. Occasionally, during a febrile illness, the ataxia becomes more evident. At his most recent examination bilateral pes cavus was observed.

Patient 2

The patient's mother, currently aged 37 years, developed bilateral sensorineural hearing loss after a febrile illness at age seven years. At age 30 years she was diagnosed with mild bilateral optic nerve atrophy. Her most recent neurological examination revealed areflexia, slight gait instability, and bilateral pes cavus.

Patient 3

The other brother, currently aged nine years, was assessed for delay in reading and writing skills when he was seven-years-old; his intelligence was normal. His neurological examination showed generalized areflexia and slight instability in tandem gait. Audiometry and brainstem auditory evoked potentials were normal. Mild hypermetropia was the only ophthalmologic finding. One year later, at a routine ophthalmologic follow-up, pale optic discs were observed. He has never experienced acute ataxia.

The clinical signs of Patient 1 were compatible with those reported in individuals with CAPOS. A targeted genetic study identified the mutation c.2452G>A in *ATP1A3* in a heterozygous state. The same mutation was subsequently confirmed in his mother and brother.

Discussion

The CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss) was first identified in three family members by Nicolaides[1] in 1996. In 2014, Demos et al.[2] reported two more affected families and reassessed the original one described by Nicolaides. They performed whole exome sequencing in

TABLE 1.
Ancillary Investigations Performed in the Patient

Investigation	Results
Neurophysiological Studies	Electromyography and peripheral nerve conduction studies: normal Electroencephalography: normal Visual evoked potentials: bilaterally delayed P100 latencies
Neuroimaging	Brain and spinal cord MRI: normal
Heart	Electrocardiography and echocardiogram: normal
Blood testing	Complete blood count: normal Glucose, lactate, transaminases, lactate dehydrogenase, urea, creatinine, electrolytes, calcium, phosphate, creatine kinase: normal Acid-base equilibrium: normal Blood culture: negative Alfa-fetoprotein: 1.16 ng/ml (normal) Serology: herpes simplex virus IgG and IgM negative; varicella-zoster virus IgG negative Amino acids, biotinidase, carbohydrate deficient transferrin, acyl carnitine profile, Succinyladenosine (S-Ado) and succinylaminoimidazole carboxamide riboside (SAICAr) test: normal
Cerebrospinal fluid testing	Cell count: erythrocytes 0/μL, leucocytes 0/μL Glucose, proteins, lactic acid: normal CSF culture: negative Herpesvirus and Enterovirus polymerase chain reaction: negative
Urine testing	Toxicology screening: negative Organic acids: normal
Genetic testing	OPA-1 gene: microarray analysis for 118 polymorphisms and known mutations: negative Leber optic hereditary neuropathy: mitochondrial DNA testing of MTND4, MTND1, MTND6 (M64V, A72V) genes: negative Mitochondrial respiratory chain deficiency: massive sequencing of coding zones of 150 related genes: negative Trinucleotide repeat expansions of SCA1, SCA2, SCA6, SCA7, and DRPLA genes: normal Genes related to hypoacusia: connexin 26, Q829X mutation (OTOF gene), Mohr-Tranebjaerg syndrome-related genes