nificant known genetic risk factor in PD, multiplying the risk of developing PD by 20 with respect to non-carriers.[4] Mutations in the *ATP13A2* gene are responsible for severe parkinsonism with good response to levodopa (Kufor-Rakeb syndrome or PARK9). Heterozygous mutations of this gene have been associated with greater predisposition to PD due to the loss of enzyme function, which causes alterations to intracellular zinc homeostasis.[5] The resulting lysosomal dysfunction leads to greater accumulation of α-synuclein.[6] Furthermore, the function of cathepsin D, a protease active in the lysosomal degradation of α-synuclein, is also diminished in the context of *ATP13A2* mutation.[7] In both enzyme defects, PD phenotype is undistinguishable from that of sporadic PD.

Our patient presented 2 mutations in genes associated with lysosomal enzyme activity that cause an impairment of lysosome-mediated autophagy and accumulation of α-synuclein in neurons. This pathogenic mechanism is an area of increasing interest in PD, not only because of its pathogenic role but also because it may represent a line of research for neuroprotective treatment.[1] We suggest that both mutations may even have a synergistic effect for the patient; the genetic study of the patient's sister would confirm the pathogenicity of both mutations; however, this was not possible.

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A new case of CAPOS/CAOS syndrome☆

Un nuevo caso de síndrome CAPOS/CAOS

Dear Editor:

CAPOS/CAOS syndrome (cerebellar ataxia, areflexia, with/without pes cavus, optic atrophy, and sensorineural hearing loss)[1] is a rare autosomal dominant genetic disorder, with only 29 reported cases according to our literature search on PubMed. It is associated with heterozygous missense mutation c.2452G>A (p.Glu818Lys) of the *ATP1A3* gene, and is characterised by episodes of neurological impairment associated with encephalopathy and weakness. The syndrome usually manifests at an early age following an acute episode of fever.[2]

We present a new case of de novo CAPOS/CAOS syndrome associated with the previously mentioned *ATP1A3* mutation, and review the available literature on the topic.

Our patient is a 46-year-old woman, the first of 2 siblings (the other sibling is a 40-year-old man, who is asymptomatic); she was born to non-consanguineous parents. She had no relevant personal history. She came to our hospital due to optic atrophy with bilateral amaurosis, sensorineural hearing loss, and gait ataxia, developing progressively from childhood.

At 22 months of age, the patient had presented 3 episodes of fever within a 6-month period, with no associated infectious disease identified; she also presented partially reversible gait instability. The results of a muscle biopsy performed at the time were normal. At 5 years of age, she developed progressive hearing loss; sural nerve biopsy revealed no abnormalities. Around the age of 10 years, she presented another episode of high fever with no apparent focus of infection, associated with muscle weakness and worsening of balance, which prevented her from walking and performing fine motor tasks. She partially recovered from this episode, remaining stable until the present time. Lastly, at age 12 she presented progressive loss of visual acuity, associated with bilateral optic atrophy.

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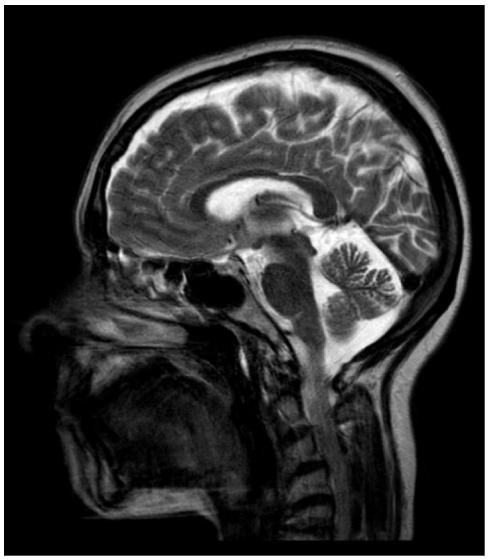

Figure 1 Brain T2-weighted MRI scan, sagittal plane, showing mild cerebellar atrophy for the patient's age.

Our examination revealed bilateral anacousia and amaurosis, bilateral atrophy of the optic papilla, bilateral horizontal nystagmus with preserved saccades, mild weakness of the palpebral orbicularis muscle bilaterally, mild hypotonia predominantly in the upper limbs and paresis (4+/5) of the shoulder girdles and hips, universal areflexia, extensor plantar reflex in the right foot and slightly extensor plantar reflex in the left, mild-to-moderate upper- and lower-limb dysmetria, truncal ataxia, wide-based gait, and positive Romberg sign.

An MRI scan of the lower limbs revealed no muscle alterations, and a brain MRI scan only displayed mild cerebellar atrophy, greater than that expected given the patient's age (Fig. 1).

A neurophysiological examination including electroneurography and electromyography studies revealed no abnormal findings.

A genetic study of mitochondrial myopathies (analysis of mitochondrial DNA plus a mitochondrial and nuclear gene panel) yielded negative results. An optic atrophy panel identified a heterozygous mutation in exon 18 of the *ATP1A3* gene (NM_152296): c.2452G>A; p.Glu818Lys. This mutation is described as pathogenic in the database consulted (ClinVar) and is responsible for CAPOS/CAOS syndrome, following an autosomal dominant inheritance pattern.[2] The family segregation study showed that the mutation appeared de novo in our patient; this therefore constitutes a sporadic case of CAPOS/CAOS syndrome.

The patient's clinical status stabilised, and symptoms have presented no further worsening to date.

Discussion

CAPOS/CAOS syndrome (OMIM #601338) is a rare entity first described by Nicolaides et al.[1] in 1996; the name of the syndrome is an acronym of the associated symptoms. In 2014, Demos and van Karnebeek[3] described an association between the condition and *ATP1A3* variant c.2452G>A (p.Glu818Lys) in heterozygosis.

ATP1A3 encodes ATPase Na^+/K^+ transporting subunit $\alpha 3$, which is mainly expressed in the cochlea, optic nerve, cerebellar cortex, and nerve fibres innervating muscles; this largely explains the clinical characteristics of the disease.[4]

In addition to CAPOS/CAOS syndrome, a rare entity compared to the classic phenotypes, other neurological diseases have been associated with mutations in the *ATP1A3* gene, showing different clinical phenotypes, such as alternating hemiplegia of childhood (OMIM #614820) and rapid-onset dystonia-parkinsonism (OMIM #128235). In the last 2 years, such other phenotypes as early infantile epileptic encephalopathy, relapsing encephalopathy with cerebellar ataxia, rapid-onset ataxia, early-onset autonomic seizures, and paroxysmal asymmetric dystonic arm posturing have also been reported. However, the group of diseases associated with mutations in the *ATP1A3* gene will continue to expand. Some authors have suggested that these disorders may represent a phenotypic continuum rather than distinct allele diseases.[5]

Symptoms typically appear during childhood. Patients present episodes of ataxia induced by fever; encephalopathy and muscle weakness appear in some cases. During this stage, patients may present encephalitis or atypical symptoms of Guillain-Barré syndrome.[2] Ataxia usually improves after the acute episode, although some patients may not recover completely. All the patients described to date have presented 1-3 acute episodes.

The least consistent feature of the syndrome is pes cavus, which is absent in up to 70% of cases (as in our patient); this has led some authors to use the term CAPOS/CAOS syndrome.[6] Many patients do not present signs of myopathy or neuropathy in complementary tests; this was the case with our patient.

Given the clinical heterogeneity of the disease and its overlap with other disorders, differential diagnosis should include syndromic dominant optic atrophy and other mitochondrial respiratory chain disorders.

There is no specific treatment for CAPOS/CAOS syndrome. We suggest using acetazolamide, mainly to prevent or reduce neurological symptoms during acute episodes of fever. The action mechanism of this treatment is based on the inhibition of carbonic anhydrase, decreasing extracellular pH, which seems to be associated with better Na^+/K^+-ATPase function.[4]

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Cardiac cephalalgia: when myocardial ischaemia reaches the neurologist's consultation*

Cefalea cardíaca: cuando la isquemia miocárdica llega a la consulta del neurólogo

Dear Editor:

Within the causes of secondary headaches, there is a subgroup associated with disorders of homeostasis, with an underlying process of variable severity sometimes being the only manifestation. This clinical scenario is frequent among elderly patients, and may represent a diagnostic challenge. This is the case for cardiac cephalalgia; it is important to recognise this rare entity as it is also an anginal equivalent.

We present the case of a 74-year-old woman with history of hypertension, type 2 diabetes, and dyslipidaemia, who was attended at the emergency department due to a 3-week history of headache. Pain was intermittent and triggered by mild effort, for instance while walking on flat ground (she was previously able to do this without exertion), and remitted with rest. Headache started in the vertex and radiated bilaterally to the frontal and lateral cervical areas. Pain was oppressive, of moderate intensity, and responded poorly to oral analgesia with paracetamol. The patient did not present hypersensitivity to sound or light and was not awakened by pain; pain was not exacerbated with Valsalva manoeuvres. The patient presented no other associated neurological or systemic symptoms, including chest pain. She visited the emergency department on 3 occasions, and headache improved with rest and intravenous analgesia (metamizole, dexketoprofen, or paracetamol). No preventive treatment was indicated. The day before her last visit, headache progressed and manifested even during rest; the pain increased in intensity and was accompanied by nausea and vomiting.

Results from the neurological and physical examination were normal. Laboratory analysis showed leukocytosis (16 870 cells/mm^3) with a predominance of neutrophils, C-reactive protein at 5.17 mg/mL, aspartate transaminase at 723 IU/L, alanine aminotransferase at 623 IU/L, LDH levels of 702 IU/L, and prolonged activated partial thromboplastin time (84 seconds). A CT scan revealed no abnormalities. Given the suspicion of headache associated with systemic diseases, we requested an ECG, which showed ST segment elevation in the inferior and lateral side (Fig. 1), and a cardiac profile test, which detected troponin T levels of 2626 ng/L (normal level: < 14 ng/L). Immediately after, the patient became haemodynamically unstable and was transferred to the coronary care unit with a diagnosis of acute inferior-posterior-lateral myocardial infarction (Killip class IV), ischaemic hepatitis, and associated mild bleeding disorder. An emergency coronarography revealed 3-vessel disease with occlusion of the right coronary artery. All lesions were revascularised with pharmacoactive stents, and individualised treatment was started with dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) and anticoagulation with acenocoumarol (due to presence of an apical thrombus in the right ventricle). At discharge the patient presented a left ventricle ejection fraction of 30% and a New York Heart Association functional classification of II, and was able to make moderate efforts with no headache relapse at 6 months of follow-up.

The term cardiac cephalalgia was first coined by Lipton et al.[1] in reference to cases of headache triggered by physical exercise in the context of myocardial ischaemia. According to the third edition of the International Classification of Headache Disorders, cardiac cephalalgia is a migraine-like headache, usually but not always aggravated by exercise, occurring during an episode of myocardial ischaemia. It is relieved by nitroglycerine. Diagnosis is supported by pain of moderate or severe intensity and in association with nausea but not sensitivity to sound or light. No more probable alternative cause should exist.[2]

Cardiac cephalalgia is a very infrequent entity. Bini et al.[3] reviewed and analysed the clinical characteristics of the 30 clinical cases published in English-language articles. Mean age was 62.4 years (range, 35-85); by sex, 63.3% of patients were men and 36.7% were women. Pain location and characteristics were varied, resembling a migraine or tension-type headache associated with physical exercise or stress, but also manifesting during rest. Most patients also presented typical chest pain or another anginal equivalent; however, headache was the only symptom in 27% of cases (particularly in elderly patients).[3] As in our case, it is likely that diabetic dysautonomia would

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