A MAN WITH CHRONIC COUGH AND ATAXIA

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62 years old, right-handed.

Patient began to present symptoms at 50 years old with gait imbalance, without incoordination or tremor in hands, slowly progressive. After a few years, he developed dysarthria, which progressively worsened, today being quite evident, and progressive numbness in the feet, with tingling, distal anesthesia, and greater disequilibrium in the dark. He mentions that sometimes his vision is "blurred", despite denying oscillopsia. He also reports a chronic cough for 20 years, with previous investigation without etiological diagnosis for cough or ataxia. He has a younger sister who developed the same symptoms at age 46. No other relatives affected. He performed an extensive genetic research for spinocerebellar ataxias (SCA 1 , 2, 3, 6 ,7 ,8 ,10, Friedreich ataxia, FXTAS) which was inconclusive.

Neurological exam:

Wide-based gait, ataxic, inability to walk in tandem, difficulty in walking on his toes and heels, markedly worse from eyes closed.

Romberg positive.

Symmetrical pupils, photoreactive, no retinal abnormalities.

He had slow pursuit broken horizontally, no skew deviation or ophtalmoparesis, downbeating nystagmus was present.

Positive head impulse bilaterally.

Other cranial nerves were normal

Strength 5/5 overall, no subtle motor deficit

Normal tone, without spasticity.

Reflexes 2+/4 in upper limbs, patellar 1+/4 and Achilles abolished

bilaterally.

Painful hypoesthesia in lower limbs up to knees, with distal apalesthesia, and

hypopalesthesia to the patella bilaterally.

Mild appendicular ataxia in upper limbs and lower limbs, axial ataxia more

proeminent, with evident cerebellar dysarthria.

Cognition was preserved

Additional exams:

Brain MRI: vermian atrophy.

Video HIT: bilateral vestibular arreflexia

ENMG: non-length dependent sensorial neuropathy (neuronopathy)

1- What is this patient syndrome?
2- What gene is probably responsible for this diagnosis?

The patient presented biallelic AAGGG repeat expansion on gene RFC1 (1500 repeats) detected on RP-PCR and confirmed on Southern Blot. His sister also showed de biallelic expansion, while his unaffected niece shows heterozygous expansion.

This result confirmed the diagnosis of CANVAS.

Biallelic intronic expansions in RFC1 have been recently recognizes as the underlying cause of CANVAS. This is an autosomal recessive, neurodegenerative disease which the phenotype can range from typical cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), to more limited phenotypes involving predominantly or exclusively one of the systems involved in balance control[1]. Patients usually begin symptoms after 35 years old. Other clinical features, such as spasmodic cough, dopa-responsive Parkinsonism and dysautonomia can also be present[2]. Cough can be reported up to three decades before any neurologic symptoms develop. Gastroesophageal reflux may coexist[1].

The estimated prevalence of *RFC1* CANVAS / spectrum disorder ranges from 1:20,000 to 1:625[1]. Although Brazilian data is scarce, it is believed that RFC-1 related disorders are frequent cause of late onset progressive ataxia[3].

Treatment is supportive with multidisciplinary team of relevant specialists such as neurologists, occupational therapists, physical therapists, physiatrists, and (depending on individual needs) speech therapists, respiratory therapists, nutritionists, and gastroenterologists[1].

References

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