

A rare case of hereditary ataxia: Gordon Holmes syndrome

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ABSTRACT

Gordon Holmes syndrome is an extremely rare, autosomal recessive condition with characteristic features of cerebellar progressive ataxia, cerebellar atrophy, and hypogonadotropic hypogonadism, which was first described in 1908 by the British neurologist of the same name. Two genes have to date been frequently associated with this syndrome, RNF216 and PNPLA6.¹ A 23-year-old man presented with secondary sexual character deficiency and progressive difficulty in gait persisting for several years. He was eventually immobilized after seven years of ongoing symptoms and was definitively diagnosed with Gordon Holmes syndrome after genetic testing revealed RNF216 gene mutation.

Key words: Cerebellar ataxia, ubiquitin, RNF216, neuro-endocrinology

INTRODUCTION

Gordon Holmes syndrome, an autosomal recessive, adult-onset condition marked by progressive cognitive decline, dementia, ataxia, and chorea, in addition to hypogonadotropic hypogonadism, was first described by the British neurologist of the same name in 1908.¹ Holmes made major contributions to the study of cerebellar physiology and challenged the current conventional ideas regarding the unitary physiology of the cerebellum, even during the First World War, when he served as consultant neurologist to the British Army on the Western Front. He was subsequently awarded the CMG and CBE and was knighted in 1951. After the war, he published comprehensively in the field of neurology, and was actively engaged in neurological practice, research and education.²

Several studies have shown that the initial symptoms of this syndrome appear in early adolescence and present as difficulty in speaking.³ Mutations in either the RNF216 or PNPLA6 genes are thought to represent the underlying cause of Gordon Holmes syndrome, although there are rare instances in which no mutation has been identified. The underlying pathophysiology involves mutations in these particular genes, which cause ubiquitin to bind to healthy proteins and induce apoptotic processes, leading to cell death.⁴ This cell death may lead to progressive ataxia, hypogonadotropic hypogonadism, and structural changes in the brain such as cerebellar atrophy and white matter lesions.⁵

However, due to its rarity and frequent misdiagnosis, the prevalence of Gordon Holmes syndrome remains unknown.

A SHORT OVERVIEW OF THE RECENT LITERATURE ON GORDON HOLMES SYNDROME

Gordon Holmes syndrome, also known as autosomal recessive spinocerebellar ataxia type 16 (SCAR16), was first described in 1908.⁶ Although nearly 110 years have since passed, to our knowledge there are still only 10 case reports in the literature. The most recent reported case is located in India with homozygous mutation for RNF216, a 30-year-old male patient with progressive ataxia and hypogonadotropic hypogonadism.⁷ Neuroimaging in that case revealed hyperintensities in the white matter in FLAIR-MR images.⁸ Chiu et al.⁹ described a patient from Taiwan with cerebellar ataxia and mutation in STUB1, another gene that can lead to Gordon Holmes syndrome. In 2019, another case was reported exhibiting classic Gordon Holmes syndrome symptoms of ataxia, amenorrhea, and cerebellar syndrome.¹⁰ That case was similar to that of a 26-year-old man reported in 2008, who presented with slowly progressing loss of balance and speech difficulty with hypogonadotropic hypogonadism.¹¹ However, the diagnosis was unfortunately not confirmed by

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