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Case Report

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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.

Keywords: Cerebellar ataxia, ubiquitin, RNF216, neuroendocrinology

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.[2] 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.[1] 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.[2] 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 hypogonadotrophic hypogonadism.[5] Neuroimaging in that case revealed hyperintensities in the white matter in FLAIR-MR images.[3] Chiu et al.[6] 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.[3] That case was similar to that of a 26-year-old man reported in 2018, who presented with slowly progressing loss of balance and speech difficulty with hypogonadotropic hypogonadism.[1] However, the diagnosis was unfortunately not confirmed by

genetic testing, indicating the critical importance of genetic testing for hereditary syndromes characterized by cerebellar ataxia multisystem presentation.[1]

CASE

A 23-year-old man presented to his family physician prior to military duty and was referred to our neurology clinic for further evaluation because of ataxia. In 2018, he was admitted to the endocrinology clinic with growth retardation and gynecomastia, as well as hypogonadotropic hypogonadism, resulting in a decision to initiate monthly sustanon therapy, which proved to be ineffective. His detailed clinical history revealed a progressive speech disorder beginning at the age of 18, along with difficulties in walking and ataxia over the following two years that resulted in an inability to walk without assistance. The patient was born by the spontaneous vaginal route, with no consanguinity between his parents and no personal history of birth trauma or neurological disease. Neurological examination revealed hyperactive deep tendon reflexes in the lower limbs with relatively preserved upper deep tendon reflexes. Cerebellar examination revealed dysmetria, dysdiadochokinesia, and dysarthria, as well as a pathological tandem gait marked by wide-step walking. Routine blood tests were normal, but hormonal tests revealed hypogonadotropic hypogonadism and low follicle-stimulating hormone, luteinizing hormone, and testosterone levels (Table).

Table. Patient's blood test results

Parameters	Results	Reference values
FSH	<0.30 mIU/mL	1.9-18.9 mIU/mL
LH	<0.07 mIU/mL	1.7-9.6 mIU/mL
GH	0.16 µg/L	0.003-0.971 µg/L

(FSH: Follicle-Stimulating Hormone LH: Luteinizing Hormone GH: Growth Hormone)

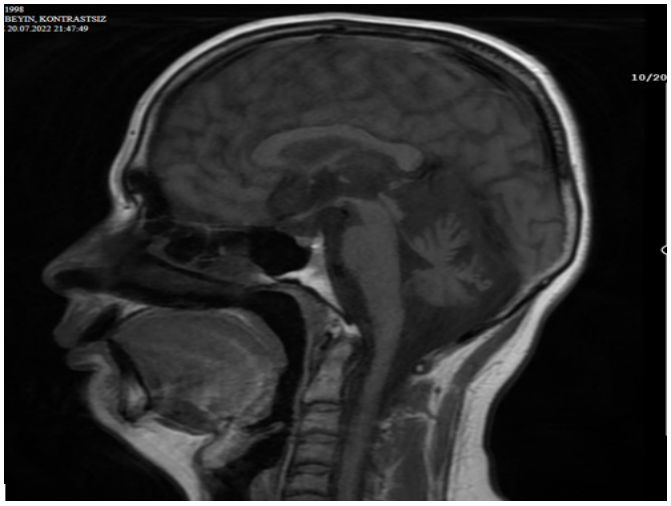

Figure 1. Magnetic resonance image without contrast showing aberrant cerebellar atrophy

An increased amount of cerebrospinal fluid was observed around the cerebellum and between the cerebellar folia (cerebellar atrophy), the third and lateral ventricles were enlarged, and hyperintense signal changes consistent with gliosis areas were present in bilateral periventricular white matter. Subsequent genetic testing revealed a homozygous RNF216 mutation.

The patient was in followed-up in the neurology and endocrinology outpatient clinics for three-month periods. Patient was informed and written consent was obtained.

DISCUSSION

Cerebellar ataxia is fairly common complaint in neurological outpatient clinics, and usually results from infections, cerebrovascular diseases, metabolic imbalances, and genetic causes.[1,9] Gordon Holmes syndrome is one of the rare genetic causes of cerebellar ataxia, and is inherited in an autosomal recessive manner due to mutations in specific genes, such as RNF216, PNPLA6, STUB1, and OTUD41; From the pathophysiological perspective, these mutations lead to the activation of the ubiquitination cascades8, triggering a proteolytic/apoptotic process, finally presenting with slowly progressing ataxia, cerebellar atrophy, dementia, and hormonal changes characterized by hypogonadotropic hypogonadism (Figure 2).[1,4]

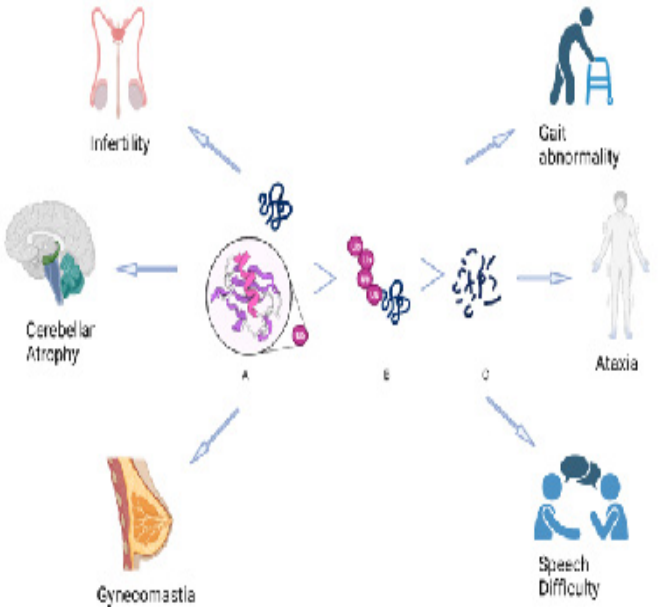

Figure 2. The ubiquitination process in Gordon Holmes syndrome, A: A healthy protein and ubiquitin, B: Ubiquitin binds to healthy protein and causes degradation of the protein C: Protein degradation and the symptoms of Gordon Holmes syndrome.[10]

Several studies have shown that the underlying pathophysiology also causes neurodegeneration in numerous regions of the brain, such as white matter, the hippocampus, and the pituitary gland.1 In our case, we found a homozygot RNF216 mutation (c.1860_1861dupCT) which caused hypogonadotrophic hypogonadism, progressive ataxia which leads to walking difficulties and white matter hyperintensities.

THE PATHOPHYSIOLOGCAL IMPORTANCE OF RNF216 (RING FINGER PROTEIN 216) GENE IN GORDON HOLMES SYNDROME

RNF216 is an E3 ubiquitin ligase, also known as TRIAD3, which regulates cell death and is one of the genes responsible for Gordon Holmes syndrome.[4] It also deserves greater attention for a better understanding of the pathophysiology of the disease. Recent studies have suggested that RNF216 is an important gene for meiosis, implicated in spermatogenesis

and the male reproduction system.[7] Melnick et al.[4] studied tissue RNF216 concentrations in rodents and found that expression commenced at one week, being observed in most tissues, including the heart, liver, and lung, with the highest levels being found in the testis. Those authors also found that RNF216 was only crucial for male reproduction, since the mutations seemed to have no effect on females.[4] As shown above, RNF216 can be detected in numerous tissues, including the central nervous system.[4,8] A good example is a recent study by Chen et al.[7], who evaluated the role of RNF216-mediated cell death in patients with subarachnoid hemorrhage and observed increased RNF216 in subarachnoid hemorrhage leading to neuronal damage. Those authors also noted that reducing the expression of the gene protected the neurons from apoptosis and lowered the level of brain injury.[7] It should also be remembered that RNF216 mutation can cause Huntington-like disorder. A case report of Huntington-like disorder with RNF216 gene mutation described patients from two Belgian families who presented with Huntington-like chorea.[4] The authors noted a distinction in terms of inheritance, with a Huntington-like phenotype occurring if the mutation is monogenic, whereas oligogenic inheritance leads to Gordon Holmes syndrome. In addition to its role in reproduction and neuronal systems, RNF216 is also involved in malignancy processes. For instance, Xie et al.[8] observed overexpression of RNF216 in glioblastoma multiforme specimens, which may be indicative of poorer prognosis.

This case report describes a 23-year-old man who presented to our outpatient clinic with progressively worsening difficulty in walking over the previous five years and who was diagnosed with Gordon Holmes syndrome with RNF216 mutation.

There are currently no therapeutic options available for the syndrome, with the exception of symptomatic treatments such as hormonal therapy, which lead to only partial improvement in some patients.1

CONCLUSION

To summarize, we describe a patient with Gordon Holmes syndrome which is a rare disorder manifested with ataxia and hypogonadotropic hypogonadism, reported from Turkiye and one which adds to our knowledge of the ethnic distribution of the RNF216 mutation, along with a brief review of the subject.

ETHICAL DECLARATIONS

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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