CASE REPORT

Rare case of Gordon Holmes syndrome

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SUMMARY

Young-onset cerebellar syndromes are quite interesting and challenging for treating clinicians. While dealing with such cases, a clinician should be aware of rare possible causes too. We report a rare case of Gordon Holmes syndrome—an autosomal recessive cerebellar ataxia with endocrinal abnormalities.

BACKGROUND

Gordon Holmes, a renowned British neurologist, first described this familial neurodegenerative disorder as autosomal recessive adult-onset, with characteristic clinical features of progressive cognitive decline and ataxia, and variable movement abnormalities. This neurological presentation was also associated with hypogonadotropic hypogonadism. He reported four patients (three brothers and one sister) from a single family of eight people who, in their mid-30s, developed progressive signs and symptoms of cerebellar disease with lack of secondary sexual characters.¹

CASE PRESENTATION

A 26-year-old married man presented to neurology department with insidious-onset gradually progressive gait and balance worsening of 4 years' duration. He had difficulty in walking in narrow passages and lurching on either side. Over the past 2 years, he had symptoms of incoordination in upper limbs and had also developed change of speech. He also complained of generalised tiredness and disinterest while performing routine activities. He was born of non-consanguinity at full term, normal delivery. There was no history of birth trauma or cryptorchidism, nor a family history of neurological disease. On examination, his vital parameters were stable. His higher mental function and cranial nerve examination were normal. His speech was scanning cerebellar type. Visual acuity, funduscopy and ocular movements were normal. Bilateral gaze-evoked horizontal nystagmus was seen. Jerky pursuits and hypermetric saccades were demonstrable. Incoordination and cerebellar signs were present bilaterally in all four limbs, with finger-nose and heel-shin evident. He had a broad-based gait, with tandem walk impaired and lurching on either side on walking. Romberg's test was negative. Motor power, tone and reflexes, and sensory examination were all normal. A diagnosis of pan-cerebellar ataxia was made and the patient was investigated for the same.

On general examination, there was lack of secondary sexual characters. The patient had sparse

hair in the axilla and pubic regions, micropenis and small size testis, mild gynecomastia (figure 1A,B) and his voice was soft, lacking the deep, husky character of an adult voice. He was married for 5 years now, but did not have any children.

INVESTIGATIONS

His routine blood reports were normal. Endocrine work-up was suggestive of hypogonadotropic hypogonadism, low Follicle Stimulating Hormone, Luteinizing Hormone, testosterone and oestrogen levels. MRI brain showed significant cerebellar atrophy, with age-inappropriate cerebral atrophy along with subcortical white matter changes (figure 1C,D). The rest of the work-up for chronic cerebellar ataxia was negative.

TREATMENT

We made a provisional diagnosis of Gordon Holmes syndrome and started him on hormonal supplements.

OUTCOME AND FOLLOW-UP

The patient had partial improvement on follow-up after 3 months.

DISCUSSION

Patients with cerebellar ataxia are quite frequently encountered in neurology wards. Young adults presenting with cerebellar syndromes are usually

Figure 1 (A) Testicular atrophy and absence of pubic hair. (B) Gynecomastia. (C, D) T2 FLAIR and T1-weighted images showing diffuse cerebellar and penduncular atrophy.

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due to infections, drug toxicity, metabolic disorders, space-occupying lesion, inherited disorders and so on. Approach to ataxia, especially in young adults, is challenging and the diagnosis turns out to be quite interesting.

In our case, the patient had progressive cerebellar syndrome without any features suggestive of cognitive decline, sphincter involvement or any involvement of peripheral nervous system. It was on detailed examination that we found the patient had features of arrested puberty and absence of secondary sexual characters. The diagnosis of Gordon Holmes syndrome was suspected due to the rare combination of ataxia and hypogonadotropic hypogonadism.

This syndrome of progressive ataxia, cognitive decline and hypogonadotropic hypogonadism is caused by mutations in RNF216 or a combination of mutations in two genes—RNF216 and OTUD4.^{2,3} The elegant study revealed that TRIAD 3A variants at two sites (R660C, R694C) resulted in loss of function, protein homeostasis and synaptic dysfunction in Gordon Holmes syndrome.⁴

This suggests the role of abnormal ubiquitin in neurodegeneration and reproductive system dysfunction. The pathological

effects of this are seen in various regions of the central nervous system including cerebellum, cerebral white matter, hippocampus, pituitary gland and the hypothalamus, hence, the combination of central nervous system and reproductive system involvement. There are reports suggesting that impaired pituitary gland release of gonadotropins is found in most patients with this syndrome.^{3,5}

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Learning points

- ▶ Gordon Holmes syndrome is a rare subtype of chronic cerebellar ataxia, infrequently reported in literature.
- ▶ The syndrome should be considered if chronic ataxia is associated with reproductive abnormalities.
- ▶ The meticulous clinical approach for chronic ataxia is required to pinpoint precise diagnosis.

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