1. Introduction

Hereditary cerebellar ataxia is a heterogeneous group of diseases. An accurate diagnosis of this disease is challenging for clinicians. Here, we report a patient with DNMT1 mutation who presented with mid-age onset of cerebellar ataxia, sensorineural hearing loss, and pyramidal signs. Moreover, additional abnormalities were reported in the central nervous system, optic nerve, and endocrine system. These features may be regarded as clues for accurate disease diagnosis.

2. Case report

A 43-year-old woman presented to our neurology clinic with unsteady gait and hearing loss for 13 years. At the age of 31 years, she experienced bilateral hearing loss. At the age of 34 years, she developed bilateral action tremor of hands. At the age of 38 years, she began experiencing difficulty walking because of ataxic gait. Horizontal head tremor began at the age of 41 years. Additionally, she had young-age onset hypertension and secondary amenorrhea in her 30s. She had knee buckling and head nodding several times per week. She was born of non-consanguineous marriage. Her parents and two younger sisters had no spastic paraparesis, cerebellar ataxia, or hearing loss. Her father passed away due to stroke over 10 years ago, and her youngest sister had mental retardation and primary amenorrhea (Fig. 1A).

Examination revealed that the patient had decreased visual acuity in both eyes, and fundoscopy revealed pale discs with an elevated cup-to-disc ratio in both eyes, suggesting optic atrophy. Hypermetric saccades were observed in all directions. No subjective sensation of hearing was observed through either air or bone conduction. The manual muscle power test revealed full and symmetric function. The biceps and knee jerk reflexes were both brisk, but the ankle jerk reflexes were absent. Dystymria, symmetrical bradykinesia, and cogwheel rigidity were found in the four limbs. The gait was wide-based, with festination and decreased arm-swing such that she failed to perform tandem gait. In summary, the patient had deficits in multiple neurological systems, including optic and auditory nerves and pyramidal, coordinating, and extrapyramidal systems.

Electrophysiological studies revealed that visual evoked potentials were attenuated with prolonged latencies in both eyes, and brainstem auditory and somatosensory evoked potentials were also attenuated. The nerve conduction study results were normal. Notably, electroencephalography (EEG) revealed frequent transient generalized rhythmic slow waves at 2–5 Hz (Fig. 1B). Magnetic resonance imaging showed diffuse atrophy in the cerebrum and cerebellum without a significant signal change (Fig. 1C-E). Serological examination revealed non-significant findings for complete blood count, electrolytes, liver and kidney function, vitamin B12, copper, ceruloplasmin, thyroid, parathyroid, and adrenal hormone levels. Estradiol was low (31.3 pg/mL), and progesterone was undetectable. Moreover, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were low, which is compatible with hypogonadotropic hypogonadism.

Genetic tests detected no abnormalities such as spinocerebellar ataxia type 1, 2, 3, 6, 7, 17, and dentatorubral-pallidolysian atrophy. Whole exome sequencing revealed a heterozygous missense mutation in DNMT1 c. 1732G > A (p.E578K), which is the causative gene for autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN). This mutation is not recorded in the ClinVar database, but the Sorting Intolerant from Tolerant database indicated that the mutation impairs protein function. (Supplementary Table 1) On the basis of the Interpretation Guidelines, this variant was classified as likely pathogenic (PM1, PM2, PM6, PP2, and PP3). Her mother and youngest sister did not have same mutation in DNMT1 gene. The patient had positive results in Epworth sleepiness scale, Ullanlinna Narcolepsy Scale, and Swiss Narcolepsy Scale, which were suggestive of narcolepsy with Cataplexy. (Supplementary Table 2) The phenotypic and genetic findings were compatible with a pathogenic mutation in DNMT1 gene, which was related to ADCA-DN.

3. Discussion

In this report, we presented a case with a new mutation in DNMT1 gene. The patient had adult-onset cerebellar ataxia, sensorineural hearing loss, optic nerve atrophy and pyramidal sign, but no marked narcolepsy. The combination of cerebellar ataxia, deafness, pyramidal sign, and optic atrophy indicates differential diagnoses, including cerebellar ataxia-areflexia-pes cavus-optic atrophy-sensorineural hearing loss (CAPOS) syndrome, Friedreich's ataxia (FRDA), and mitochondrial diseases [1]. Patients with CAPOS syndrome usually present with...
relapsing-remitting fever-induced acute-onset cerebellar ataxia during infancy or childhood and frequently show encephalopathy [2]. FRDA is the most prevalent recessive ataxia in the European population, whereas it accounts for only 0.8% of the total cerebellar ataxias in Taiwan [3]. The prevalence of neuropathy in FRDA, presented as loss of lower limb reflex, was 74%-99%, and auditory neuropathy affects only a significant minority [4]. Mitochondrial diseases may involve multiple systems, as in our patient, and may lead to more detrimental manifestations, including epilepsy or myopathy, as well as significant increase in lactic acid after exercise, which did not occur in our patient. However, it can be considered as a potential etiology of our patient after excluding abnormalities in nuclear genes.

ADCA-DN is characterized by cerebellar ataxia, deafness, and narcolepsy. Optic atrophy, cataract, sensory neuropathy, and dementia may develop in the later stages of the disease. Mutation in exon 21 of the DNMT1 gene causes ADCA-DN. A nearby mutation in exon 20 of DNMT1 may cause hereditary sensory and autonomic neuropathy type 1E (HSAN-1E), presenting as a triad of peripheral neuropathy, deafness, and dementia. The EEG of HSAN-1E may reveal generalized slow waves with correspondent cognitive deficit [5]. The rhythmic generalized slow waves in the EEG of our patient suggested early involvement of encephalopathy. Patient with cerebellar ataxia and deafness, the combination of asymptomatic optic atrophy and EEG abnormality indicates ADCA-DN. Our patients had an almost typical presentation of ADCA-DN and the novel variant was classified as likely pathogenic [6].

In addition to neurological deficits similar to those reported in previous cases, our patient had amenorrhea. The decreased FSH/LH and estradiol suggested secondary amenorrhea, which was related to gonadotroph cells in the anterior pituitary gland or gonadotropin-releasing hormone (GnRH) -secreting cells in the hypothalamus. Other axes, including thyroid, adrenal, and growth hormones, were normal in our case. The selective involvement of gonadotroph or GnRH-secreting cells suggested a difference in DNA-methylation in each endocrine axis.

The inhibition of DNA methyltransferases significantly upregulated the mRNA levels of fibroblast growth factor 8, a potent morphogen that regulates the embryonic development of hypothalamic neuroendocrine cells [7]. Additionally, bisphenol A, an environmental hormone, altered the mRNA levels of DNMT1 and DNMT3A in the juvenile cortex and hypothalamus, which induced persistent sex-specific effects on social and anxiety-like behavior [8]. These findings indicate a close link between DNMT1 and sexual development. However, the correlation of DNMT1 mutation with hypogonadotropic hypogonadism needs further investigation. This report presents a case of a clinically convincing case of ADCA-DN, with intriguing hormonal disturbances which may or may not be linked to the phenotype; however the mutation remains to be verified.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2020.100271.

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