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Case report

Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) – A case report and review of literature



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ABSTRACT

CANVAS (cerebellar ataxia with neuropathy and vestibular areflexia syndrome) is a rare neurological syndrome of unknown etiology. The main clinical features include bilateral vestibulopathy, cerebellar ataxia and sensory neuropathy. An abnormal visually enhanced vestibulo-ocular reflex is the hallmark of the disease. We present a case of 58-year-old male patient who has demonstrated gait disturbance, imbalance and paresthesia of feet for 2 years. On examination ataxia of gait, diminished knee and ankle reflexes, absence of plantar reflexes, fasciculations of thigh muscles, gaze-evoked downbeat nystagmus and abnormal visually enhanced vestibulo-ocular reflex were found. Brain magnetic resonance imaging revealed cerebellar atrophy. Vestibular function testing showed severely reduced horizontal nystagmus in response to bithermal caloric stimulation. Nerve conduction study revealed loss of upper and lower limb sensory nerve action potentials. The course of illness was progressive with ataxic gait and unsteadiness as the most disabling symptoms. We report 4-year follow-up of the patient since the beginning of the disease.

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1. Introduction

Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) is a progressive, neurodegenerative disorder. Its characteristic symptoms were first described in a group of patients with vestibulopathy by Bronstein et al. [1]. Initially, the syndrome was known under the name of

cerebellar ataxia with bilateral vestibulopathy, although sensory neuropathy was already then observed in the majority of patients. It was not until 2011 when Szmulewicz et al. introduced new name for this condition – cerebellar ataxia, neuropathy and vestibular areflexia syndrome, CANVAS, including neuropathy as the core feature [2].

The age of onset is between 50 and 60 years. Although the syndrome has been considered as sporadic, an idea of late-onset

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autosomal recessive pattern of inheritance arose after it was described in two pairs of siblings [2,3]. The disease seems to affect male and female with similar frequency [3]. The data on epidemiology of CANVAS are lacking because the disorder is rare. In addition, it is likely to be underdiagnosed due to the fact that (1) usually not all the symptoms are observed simultaneously, especially neuropathy may develop on later stages of the disease [2,3], (2) nerve conduction studies are not routinely performed among patients with cerebellar ataxia if clinical symptoms of neuropathy are not present on examination and (3) visually enhanced vestibulo-ocular reflex (VVOR) examination that may indicate combined cerebellar and vestibular dysfunction is not the part of routine neurological examination.

Imbalance is the most noticeable feature of CANVAS, present in all cases, in majority being a presenting sign of the syndrome. The cerebellar symptoms of CANVAS include saccadic smooth pursuit, gaze-evoked nystagmus, gait and appendicular ataxia and dysarthria. Symptoms of sensory neuropathy may not be present on clinical examination and in some cases hyperreflexia in lower limbs may be observed [3]. A sign characteristic for CANVAS and easy to check is impaired VVOR [4]. During locomotion VVOR is responsible for stabilization of gaze [5]. Examination of this reflex is possible through slow horizontal turning of patient's head from side to side while his eyes are fixed on a target. The normal eye movements should be smooth and fluent during rotations. In CANVAS patients this maneuver reveals saccadic eye movements. This is possible only if all three components of VVOR, vestibulo-ocular reflex, smooth pursuit, and optokinetic reflex are impaired. Vestibulo-ocular reflex is responsible for compensatory eye movements when a patient is turning his head left and right. Smooth pursuit is responsible for smooth compensatory eye movements during watching small objects moving from side to side. Optokinetic reflex has the same role while watching whole moving scenes, e.g. while sitting in a train and looking through a window. Optokinetic reflex has also been known as "railway nystagmus". Impairment of the VVOR during turning of the head slower than 1 Hz indicates double pathology, involving both vestibular and cerebellar pathways [4].

The etiology of CANVAS is not known. The only available post-mortem study of a patient with CANVAS revealed severe atrophy of both vestibular nerves, as well as a loss of neurons in facial, trigeminal, and vestibular ganglia, sparing the cochlear ganglion [6]. Loss of Purkinje cells in cerebellum and severe axonal loss on biopsy of sural nerve were also found [3].

Cerebellar atrophy on brain magnetic resonance image (MRI) is evident in most patients with CANVAS. While the severity varies, a consistent pattern of anterior and dorsal vermis atrophy and laterally hemispheric atrophy predominantly affecting crus 1 was observed [7]. Although the diagnosis of CANVAS is made mainly based on clinical features, MRI findings, vestibular loss in caloric stimulation test, and absence of sensory nerve action potentials (SNAPs) on sensory nerve conduction studies are helpful in diagnosis.

The major differential diagnoses include spinocerebellar ataxia type 3 (SCA3), Friedreich's ataxia, multiple system atrophy of cerebellar type (MSA-C), and Wernicke's encephalopathy [2,3,8]. SCA3 has an autosomal-dominant pattern of inheritance and symptoms can often be observed among

members of the family; however, sporadic forms are also common. Neuropathy typically affects both sensory and motor fibers. The pattern of brain atrophy in MRI is different in SCA3 compared to CANVAS, with cerebellar hemispheres intact. Up to date SCA3 has not been described in Polish population [9]. Friedreich's ataxia is the most common autosomal recessive ataxia. The main symptoms include ataxia of gait and limbs, lack of tendon reflexes and positive Babinski sign. It develops typically since adolescence till 25th year of life; however, cases of late-onset Friedreich's ataxia were also described. Genetic tests are available to confirm the diagnosis of SCA3 and Friedreich's ataxia as well. MSA-C is diagnosed when in addition to cerebellar signs, the patient presents with autonomic dysfunction such as orthostatic hypotension or urinary incontinence. Wernicke's encephalopathy can present subacutely with the classic triad of ocular motor abnormalities (including nystagmus), gait ataxia, and mental state changes, although not all of these symptoms must be present at the same time [10]. Additionally, bilateral vestibulopathy may accompany encephalopathy [11]. Wernicke's encephalopathy should be suspected among alcoholic or malnourished patients. Other causes of cerebellar ataxia (e.g. chronic alcohol ingestion), vestibulopathy (e.g. iatrogenic due to aminoglycosides), and sensory neuropathy (e.g. diabetes) should be excluded.

The course of CANVAS is progressive. Disease progression is usually slow but varies greatly between patients. Some of them are only having minor problems with locomotion few years since symptom onset, while others are bed-ridden or use wheelchair [3]. There is no cure for the disease. Physiotherapy and application of walking tools such as cane or crutch may help patient in maintaining physical efficiency and avoid complications from immobilization.

2. Case description

The patient we present is a 58-year-old male. He started to suffer from instability of gait and paresthesias of feet described as burning and tingling sensation 2 years earlier. Symptoms were experienced daily with similar intensity. He also complained about sporadic painful muscle cramps, mainly affecting muscles of the calves. On examination wide-based gait, gaze-evoked downbeat nystagmus, dysarthria, and impaired alternating rapid movements were found. Romberg's test was positive with eyes both open and closed but it was exaggerated with eyes closed. Diminished knee and ankle jerks and absence of plantar reflex were also found. Upper limb reflexes were normal and symmetric. Muscle tone was slightly diminished in both upper and lower limbs. Muscle strength was not impaired. Pin-prick and vibration sensation as well as joint position sense were normal on examination in upper and lower limbs. Compensatory saccadic eye movements instead of normally seen smooth were present while examining for VVOR. Gaze-evoked downbeat nystagmus was present.

Vestibular function testing revealed severely reduced horizontal nystagmus response to caloric stimulation test bilaterally. Audiogram result was normal. Cerebellar atrophy including both hemispheres and vermis, without any focal lesions, was shown in MRI (Figs. 1 and 2). In nerve conduction

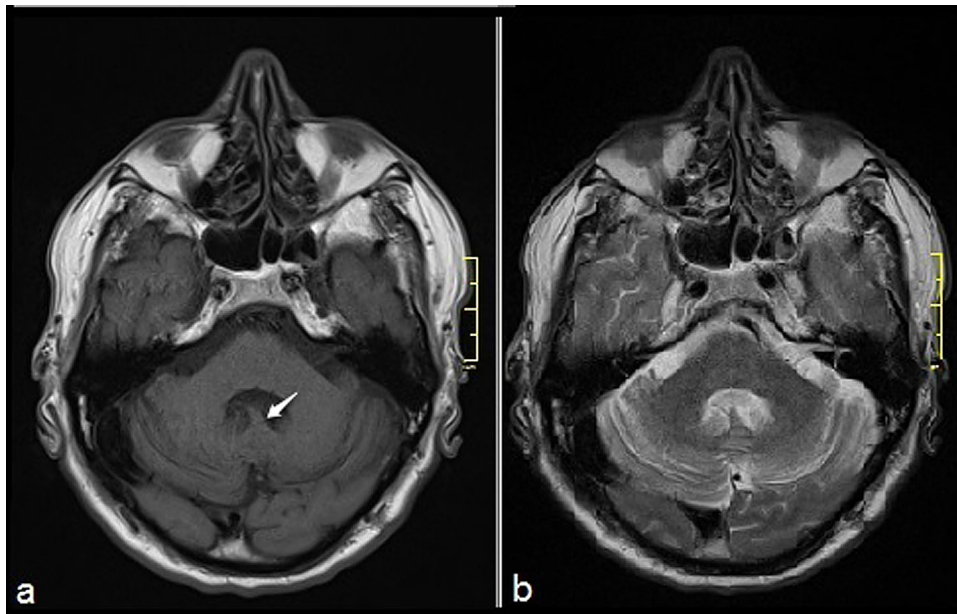


Fig. 1 – T1 (a) and T2 (b) weighted transverse images of cerebellum. Enlargement of the fourth ventricle and atrophy of the cerebellar vermis (white arrow).

study sensory nerve action potentials were not found in median, ulnar, radial, and sural nerves, bilaterally. Motor nerves conduction study was performed in right median and peroneal nerves. The amplitude of compound motor action potential (CMAP), distal latency, conduction velocity, and F-wave latency were found to be within the normal range. Quantitative, needle electromyography (EMG) was performed in the right biceps brachii, first dorsal interosseous, tibial anterior, and vastus lateral muscles. The main parameters of motor unit activity potentials (MUAPs) such as amplitude, duration and size index were found significantly increased in each of the examined muscles, suggesting neurogenic abnormalities as chronic denervation with subsequent reinnervation. The spontaneous activity at rest (fasciculation potentials) was found only in tibial anterior muscle. Other forms of

spontaneous activity, suggesting acute denervation, as fibrillations or positive sharp waves were not found. Concluding axonal sensory polyneuropathy and mild neurogenic abnormalities (re-innervation signs) in examined muscles were found in electroneurography (ENG) and EMG study.

Psychological examination revealed intact cognitive functions. Genetic tests were performed, excluding Friedreich's ataxia and SCA 3 as a possible causes of symptoms. Paraneoplastic syndrome was also excluded by Western-Blot with recombinant antigens (Hu, Yo, Ri, Ma2/Ta, and amphiphysin). Laboratory tests were normal. Causes of neuropathy such as diabetes, hypothyroidism, kidney failure, exposure to toxins or chemotherapeutics were not present in case of our patient. He was not treated with aminoglycosides in the past. The only comorbidity was hypertension, diagnosed in 2011,

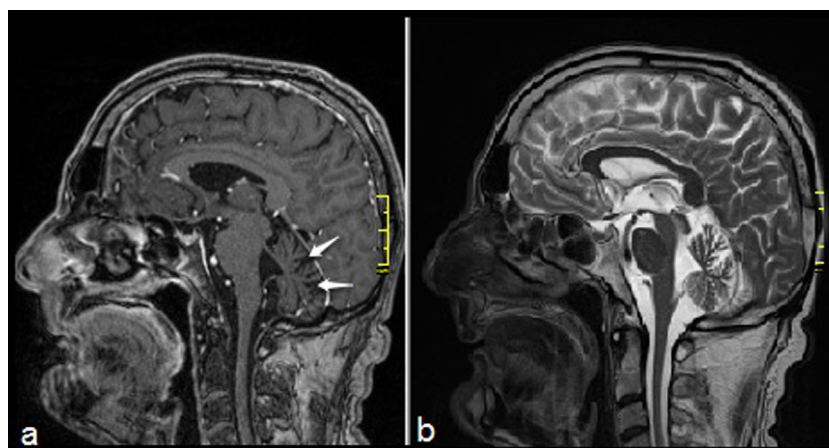


Fig. 2 – T1-weighted contrast-enhanced sagittal view of the cerebellar hemisphere (a) and T2-weighted sagittal view of the cerebellar hemisphere (b) with visible moderate atrophy (white arrows).

well controlled with clonidine. He has no history of nicotine or alcohol abuse. He worked as a railway man and due to his health problems was moved to clerical work but he is still professionally active.

The family history was negative in terms of neurodegenerative disorders or gait problems. The patient's mother suffered from diabetes mellitus type 2 and hypertension and underwent an ischemic stroke. She died at the age of 79 of undetermined cause during hospitalization. Patient's father died suddenly at the age of 79 of undetermined cause. Our patient has had no information regarding his health status. The patient has two children, son aged 36 and daughter aged 31, both healthy.

The patient was dismissed from hospital in a good condition, with recommendation of physiotherapy and follow up at outpatient clinic. He was also prescribed betahistine, but he discontinued treatment after 6 months due to lack of improvement. On the first follow up visit, 6 months later, his status showed no significant deterioration compared to discharge. However, on the second visit, 1 year since the diagnosis was made and 3 years since the beginning of the disease, deterioration of his motor function was observed. He had severe difficulties in walking due to ataxia and imbalance. His wide-based gait worsened, but he was still able to walk unassisted. The number of falls increased. The patient complained mainly of gait difficulty and painful cramps of calf muscles. Compared to previous examinations, loss of knee and ankle jerks and diminished upper limb tendon reflexes were found. Pin-prick, vibration sensation, and joint position sense were still intact. After 4 years of the disease duration he started to complain of abnormal vision in the dark and morning fatigue. Now he only reports minor deterioration of gait compared to 1 year ago but he is still able to walk unassisted. His speech did not deteriorate within the last year.

3. Discussion

We present a patient with cerebellar syndrome combined with vestibulopathy and sensory peripheral neuropathy, which suggests CANVAS as the most likely diagnosis. To the best of our knowledge, the disorder has not been yet described in Polish literature. The presenting symptom in our patient was ataxia of gait. The finding of cerebellar signs on examination seemed to be reasonable cause of his gait problems. However, due to disabling dysesthesias within distal parts of limbs and diminished reflexes, the patient was referred to conduction velocity study with suspicion of neuropathy. ENG confirmed the diagnosis of generalized axonal sensory neuropathy. Then, we started to look for the possible causes of combined sporadic cerebellar ataxia and sensory neuropathy of late onset. We came across CANVAS description and due to abnormal VVOR the patient was referred to caloric test to assess vestibular function. Vestibular areflexia that was found on the latter examination enabled us to make the right diagnosis in our patient.

The diagnosis of CANVAS is usually difficult because of one priming pathology explaining the patient's symptoms and few signs suggesting involvement of other systems. However, careful investigations may show involvement of other

systems. Kirchner et al. [8] revealed that up to 25% of the patients with bilateral vestibulopathy present also with cerebellar signs on examination. Another study, focusing on comorbidities related to downbeat nystagmus reported a considerable association with cerebellar signs, bilateral vestibulopathy, and peripheral neuropathy [12]. Such results indicate that the true incidence of CANVAS may be notably higher.

Imbalance and unsteadiness of gait are usually the first and the most disabling symptom in patients with CANVAS [2,3,5]. Imbalance is caused by damage of both systems responsible for balance control, cerebellum and vestibules. Neuropathy may also contribute to balance and gait problems due to sensory deficits. In a patient with cerebellar signs the cause of gait problems seems to be clear and a physician does not suspect that other reasons, such as vestibular dysfunction and sensory neuropathy, may contribute to unsteadiness of gait. Therefore in patients with unexplained gait ataxia special emphasis should be put on sensory deficits, limb reflexes and eye movements examination including VVOR, gaze-evoked nystagmus and vestibular function. Imbalance in patients with CANVAS is exaggerated in darkness and subsequent falls may result from cerebellar and sensory ataxia as well [8]. It is consistent with the findings in our patient. His Romberg's test was positive with eyes both open and closed but he was more unstable with eyes closed despite his joint position sense and vibration being sensation were intact. Nystagmus is another frequent symptom of cerebellar and/or vestibular involvement in CANVAS. It is commonly gaze-evoked, horizontal or downbeat. Interestingly, many patients do not report any complaints of vision disturbances due to nystagmus, such as oscillopsia [4]. The patient described by us, who had gaze-evoked downbeat nystagmus, did not have such complaints within the first 3 years of the disease.

Vestibulopathy can be observed in caloric test as absence of or reduced horizontal nystagmus during irrigation of warm (around 44 °C) water to one ear and cold (30 °C) to another [5]. Hearing is usually not impaired in CANVAS patients. Our patient had only slight response to bithermal caloric stimulation and did not have any problems with hearing that was confirmed by correct audiogram result. Although the level of vestibular injury cannot be established with caloric stimulation test, loss of vestibular response combined with normal hearing may suggest involvement of vestibular nuclei within brainstem.

Neuropathy can usually be observed clinically; however, in some cases it can be detected only by electrophysiological study. Typically it is described as sensory axonal neuropathy [2]. It is manifested by diminished reflexes, dysesthesias and abnormal proprioception. Pinprick perception and sense of vibration may also be impaired. Diminished ankle jerks are particularly common among CANVAS patients [3]. The neuropathy is more expressed in lower limbs and in distal parts of the limbs, described as "gloves and stocking" neuropathy [3]. Our patient reported burning sensations and numbness of lower limbs but also had reduced knee jerks and ankle jerks. Nerve conduction study is particularly recommended for patients with cerebellar and vestibular pathology but without clinically visible symptoms of neuropathy. Typical finding is absence of SNAPs [3]. It is hypothesized that sensory

abnormality is the result not only of neuropathy but also neuronopathy [2]. Neurogenic electromyographic abnormalities in skeletal muscles that reflect the presence of chronic denervation together with normal motor nerve conduction velocity and normal amplitude of compound motor action potentials may suggest a loss of motor neurons in the anterior horns of the spinal cord. Given the clinical and electrophysiological findings in our patient, together with the sensory spinal neuronopathy hypothesis, may indicate the involvement of spinal cord. To the best of our best knowledge lower motor neuron involvement reflected by clinical, electroneurographic, and electromyographic abnormalities was not reported in previous descriptions of CANVAS patients.

Brain MRI is used in differential diagnosis of CANVAS. Atrophy of vermis and cerebellar hemispheres is commonly observed, but this feature may not be evident in early stage of the disease. We found moderate cerebellar atrophy in our patient, which may be due to short duration of the disease (Figs. 1 and 2). Our patient was diagnosed 2 years after symptom onset in contrast to mean delay in the diagnosis that was previously described as long as 11 years [3].

Differential diagnosis in our patient included SCA3 and Friedreich's ataxia, both excluded by genetic testing, MSA-C and Wernicke's encephalopathy, both excluded by clinical symptomatology, progression rate of the disease, MRI, and vestibular test findings. We also excluded diabetes, drug-induced vestibulopathy and neuropathy, alcohol ingestion and paraneoplastic cause of cerebellar atrophy.

CANVAS is a progressive disease and the course and duration vary [3]. There is no known pharmacological treatment that can modify the natural course of disease. In our patient the progression of the disease was fast within 3 years since the beginning of the disease and remarkably slower within the last year. After 4 years of duration of the disease he can still walk unassisted, but due to unsteadiness of gait falls have become more frequent. Abnormal vision in the darkness had occurred in the fourth year of the disease duration which suggests that new symptoms may appear after a few years since the onset of the disease. Signs of sensory and lower motor neuron involvement have not been troublesome for the patient.

In conclusion, we should recommend that in patients with late onset sporadic cerebellar ataxia of unknown origin assessment of vestibular function, nerve conduction study and electromyography of skeletal muscles should be performed to look for CANVAS cases. Based on the literature and the findings in our patient, CANVAS seems to be neurodegenerative, progressive disease with cerebellum, brainstem and spinal cord involvement.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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