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A clinical case of cerebellar ataxia with neuropathy and vestibular areflexia syndrome in the presence of polycythemia vera

Cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome (CANVAS) is a slowly progressive ataxic disorder characterized by the triad of cerebellar impairment, bilateral vestibular hypofunction, and sensory polyneuropathy. The paper describes a clinical case of this syndrome in a 40-year-old patient who has been followed up by hematologists for polycythemia vera for 10 years.

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Cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome – CANVAS) – is a hereditary disease with a late onset that can be transmitted by an autosomal dominant or recessive type, the gene is not detected [1,2]. The clinical picture is determined by a variety of symptoms: cerebellar lesion, bilateral reduction of vestibular functions, and sensory polyneuropathy. Vestibulopathy is characterized by a bilateral decrease in the vestibular-ocular reflex [3,4]. Head rotation and gaze fixation tests as well as video – oculography, videonystagmography or testing on a rotating chair are used to identify the disorder. Manifestations of cerebellar disorders may be represented by speech disorders, cerebellar dysarthria as well as movement disturbance of muscular coordination – ataxia. Magnetic resonance imaging revealed atrophy of the anterior and dorsal part of the cerebellar vermis as well as the presence of atrophic changes in the cerebellar hemispheres. Neuropathy is clinically confirmed by sensory deficit represented by impaired vibration and proprioceptive sensitivity. Electroneuromyography plays an important role in diagnosis. Autopsy revealed the loss of Purkinje cells mostly in the cerebellar vermis, gangliopathy in the posterior roots of the spinal cord and the nuclei V, VII and VIII of the cranial nerves [4,5,6].

Case report

A 40-year-old patient B *was admitted to the neurological department of the clinic of the Bashkir State Medical University for the treatment as per local neurologist's referral. On admission the main complaints were inability to walk independently on the street, to cross the road due to the development of blurred vision, difficulty in assessing the distance of driving cars, weakness, lack of support and confidence when walking. He has been considering himself ill since 2007 when he first began to feel weakness in the lower limbs. Throughout the year the impaired sensitivity appeared in the feet, in patient's words «he did not feel his socks on his feet». The patient also noticed excessive sweating in the feet and hands. After some time the unsteady gait and faltering steps appeared when walking. The patient has been using a cane since 2016. He quit his job. While moving around the city, unusual and new states appeared in the form of blurred vision, difficulties in estimating the distance of driving vehicles. There is also a rapid fatigability and general weakness. The patient associated these symptoms with the diagnosis of polycythemia vera (PV) established by hematologists in 2008. For the treatment of PV the hematologist prescribed cytostatic agent – hydroxycarbomide (Hydrea®) 1,000 mg per a day with monitoring of complete blood cell count once a month, disaggregant – acetylsalicylic acid 100 mg per a day. During the examination it was revealed that the patient had not taken the recommended drugs for about six months on his own initiative. Taking into account the aggravation of neurological symptoms the patient independently visited the local neurologist at the place of residence. After neurological examination the patient was sent to the neurological department of the Clinic of Bashkir State Medical University for the planned inpatient treatment.*

Physical examination: the patient is obese (body mass index = 32,3), body height – 167 sm, balanced body build. The family history could not be traced as the patient grew up in an orphanage. The patient does not smoke. He occasionally uses a moderate amount of alcohol. The face and the neck There is a hyperemic face and neck, redness of sclera, acrocyanosis, cyanotic colour of oral mucosa. Cognitive functions are preserved. Neurological status: mild distal paraparesis of lower limbs, hypoesthesia in the distal parts of all limbs, autonomic dysfunction of peripheral type in the distal parts of all limbs, moderate static ataxia that is clinically manifested by impaired walking (a combination of cerebellar and sensitive ataxia). Bilateral decrease in the vestibular-ocular reflex was revealed with the help of Frenzel glasses. The test «stand up and walk for a while» when the patient was asked to get up from the chair, walk 3 meters, turn around and return to the starting place. Normal value is considered to be no more than 10 seconds, the examined patient spent 22 seconds which is a sign of a significant restriction of movement. Cognitive impairment was not identified during the neuropsychological examination (MMSE-30,

FAB-16, clock drawing test – 10 points). Performed clinical and laboratory studies showed erythrocytosis, thrombocytosis (erythrocytes – $6.9 \cdot 10^{12}$/l, hemoglobin – 185 g/l, hematocrit – 57%, platelets – $717 \cdot 10^{9}$/l).

Abdominal ultrasound test showed the following dimensions of the spleen: 12.6×5.5 cm, area – 50 cm^2. Taking into account a variety of schools of ultrasound diagnostic tests in medical establishments [7], both linear dimensions and the area of the largest section were measured. The results were interpreted as a slight increase in the size of the spleen.

Data of stimulation electroneuromyography (ENMG) of the lower and upper limbs performed in 2017: 1. Signs of moderate sensorimotor polyneuropathy of the lower limbs with a predominant lesion of the fibular nerves in the distal parts of myelinopathy type D = S; 2. Signs of indolent sensory polyneuropathy of the upper limbs of myelinopathy type; 3. Syndrome of cubital tunnel on both sides (disturbance of conduction myelinopathy type along the elbow nerves on both sides). According to the needle electroneurography the following was revealed: moderate degenerative changes in the muscles of the limbs, more pronounced in the proximal muscles of the lower limbs. Signs of reinnervation are recorded. Signs of activity of the degenerative process were not revealed. Data of stimulation electroneuromyography of the upper and lower limbs nerves performed in 2015: signs of a moderately pronounced sensorimotor neuropathy of axonal-demyelinating type with a predominant lesion of the lower limbs. Moderate diffuse cerebellar atrophy was determined according to the magnetic resonance imaging (MRI) of the brain performed in 2015. MRI of the brain (capacity 1.5 T) in 2018 revealed an expansion of the anterior and posterior fissure of the cerebellum, atrophic changes in the cerebellar lobes (Fig. A), diffuse cerebellar atrophy in both hemispheres of the cerebellum (Fig. B), there were no pathological changes in the periventricular areas at the level of the basal ganglia (Fig. C). An MRI of the cervical spine (2018) revealed no pathology.

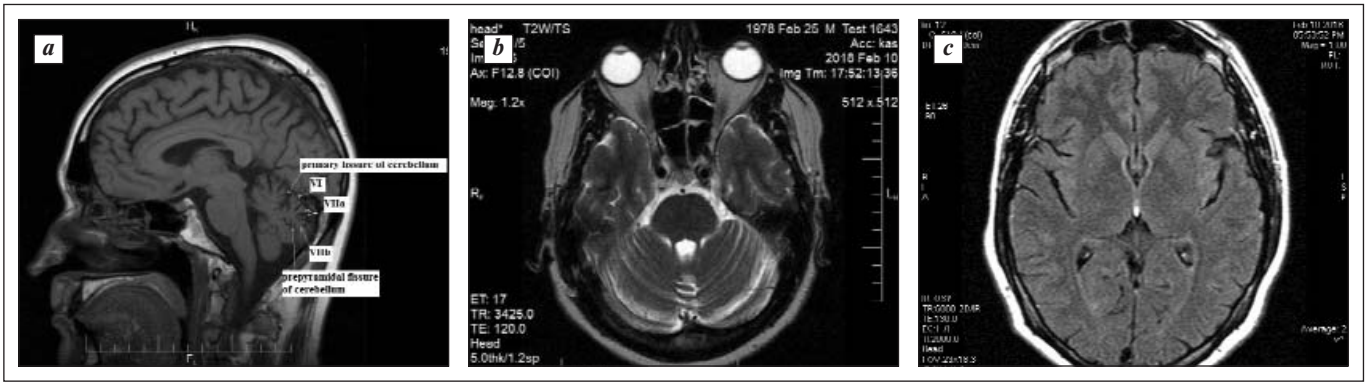
Thus, when evaluating MRI performed in 2015 and 2018 it is possible to state that the patient has the progression of neurological disease according to clinical and neuroimaging data. In this case the use of neuroimaging techniques has a great diagnostic value and allows to identify atrophic changes in brain structures and assess the dynamics of disease progression, taking into account the clinical picture of the course of the disease [8]. Ophthalmic examination: optic nerve discs of pale pink colour, clear boundaries, narrowed arteries. The veins are dilated and fully plethoric, the retina is unchanged. Intraocular pressure is 14/15 mm Hg.

Cerebellar ataxia with neuropathy and vestibular areflexia (CANVAS syndrome) was diagnosed taking into account the course of the disease with polyneuropathic syndrome (currently represented by mild distal paraparesis of lower limbs, hypoesthesia in the distal parts of all limbs, autonomic dysfunctions of the peripheral type in the distal parts of all limbs confirmed twice according to ENMG), the development of moderately pronounced static ataxia syndrome with cerebellar degeneration detected by MRI of the brain and clinically manifested as a distinct impaired gait (combination of cerebellar and sensitive ataxia), the main patient's complaint of inability to walk outside and to cross the road due to the development of lightheadedness with blurred vision (the patient with a slight distal paraparesis of legs moves with a cane for support and sure steps) , decreased vestibulo-ocular reflex. Secondary diagnosis: polycythemia vera.

In cooperation with hematologists, according to the clinical recommendations [9] for the treatment of polycythemia vera, the following therapy was carried out: acetylsalicylic acid (100 mg /day) at night, hydroxycarbamide 500 mg 1 capsule 2 times a day, blood exfusion 400 ml followed by intravenous drip 5 ml of 2% pentoxifylline solution with 400 ml of sodium chloride solution intravenously 3 infusions every other day with monitoring of hematological parameters (hemoglobin and hematocrit). In the course of the therapy the patient noted an improvement in the general health state. The skin acquired a normal colour. According to laboratory data positive dynamics was revealed represented by a decrease in the level of red blood cells – up to $4.03 \cdot 10^{12}$/l, hemoglobin – up to 132 g/l, hematocrit – up to 41.1%, a decrease in platelet count to $394 \cdot 10^{9}$/l.

Discussion

CANVAS results from the impairment of cerebellar, vestibular and sensory functions leading to progressive and severe balance impairment. The first description of a syndrome characterized by late onset axial and limb ataxia in patients with bilateral vestibular deficit with impaired visually enhanced visual vestibular ocular reflex (VVOR), and cerebellar dysfunction did not include peripheral neuropathy[10]. More recently, sensory or sensorimotor axonal neuropathy has been included as an integral part of the CANVAS' clinical pic-



MRI of the brain of the 40-year-old patient with CANVAS syndrome. A. T1 – weighted image, sagittal plane. Expansion of anterior (primary fissure of cerebellum) and posterior fissures (prepyramidal fissure), atrophic changes in cerebellar lobes VI, VIIa, VIIb. B. T1 – weighted image, there are cortical atrophic changes in both cerebellar hemispheres at axial section. C. Axial FLAIR image – no pathology detected at the level of basal ganglia

ture. The course of the disease observed in our patients, similar to those previously reported, suggested that the diagnostic suspicion of CANVAS can be based on the neurological examination. The most remarkable aspect leading to patients' disability was the severe and progressive balance impairment. This could be explained by cerebellar and vestibular dysfunctions, proprioceptive impairment caused by a nonlength dependent sensory neuropathy and VVOR impairment. These latter components seem to be the prototypical abnormality in CANVAS patients [11]. On clinical ground, they presented with gaze-evoked horizontal or downbeating nystagmus associated with saccadic breakdown of smooth pursuit and abnormal head impulse test, whose alteration is also seen in «doll's head reflex». VVOR impairment results from altered gain of smooth pursuit eye movements and vestibulo-ocular reflex which are physiologically redundant at low stimulus frequencies. This reflex stabilizes images on the retina during head movements, most efficiently at high-input velocities, by producing an eye movement in the direction opposite to head movement. Impairment of this reflex may be visible at bedside in CANVAS patients. [12].

Our patient had a characteristic clinical picture, characterized by a slowly progressive gait ataxia and impaired sensitivity in the feet, accompanied by cerebellar dysfunction. However, given the associated disease PV, this neurological dysfunction was not regarded as a course of a separate, independent disease.

Polycythemia vera (PV) – is a chronic myeloproliferative neoplasm characterized by a lesion of a stem cell. The disease is accompanied by a somatic mutation in the gene of the Janus kinase (JAK2) cytokine receptors and manifests itself by the proliferation of the myeloid hemopoietic germ with possible development of extramedullary hematopoiesis, thrombotic complications and the outcome of postpolycythemic myelofibrosis or blast transformation [13,14,15]. The incidence of PV is 1–1.9: 100,000 of the population [16, 17]. Thrombosis in 1.8% – 10.9% of patients per year, depending on risk factors [18]. At the same time, even in young patients, the cumulative risk of thrombosis is 14% with a PV duration of ten years [19]. With a prolonged course of the disease, secondary postpolycythemic myelofibrosis develops at about 0.5% per year [20]. The probability of disease progression into the blast transformation phase is 0.34% per year during the first 5 years of the disease with an increase of up to 1.1% per year with a disease duration of over 10 years [18]. Patients with PV and comorbid diseases and thrombotic complications are a difficult diagnostic group. Long-term stem cells ptoliferation result to fibrosis and bone marrow substitution with collagen fibers – postpolycythemic myelofibrosis. Some patients can get disease progression with blastic transformation. Through to recent success in molecular-genetic PV mechanisms decryption, PV diagnostic had been signifi cantly improved; also new class of drugs with pathogenic action had been developed [21,22,23].

Special treatment for CANVAS syndrome was not developed since the syndrome is a rare disease and the main biological cause of the disease will be determined in the future. In the cases published in the literature, patients with CANVAS syndrome are offered vestibular rehabilitation including various modes of movement. Components of vestibular rehabilitation are selected individually and can include training for coordinating eye and head movements, improving walking skills and gaining knowledge of awareness of body position. It is necessary to remember about the possible fall of patients while walking and thus pay attention to «safe walking» that is to recommend patients to use canes and comfortable shoes tightly fixed to the feet. When traveling along a big city it is necessary to plan a route or move accompanied, use reflective elements on clothes when crossing the road in the evening and at night. Thereby vestibular rehabilitation will significantly reduce the risk of falls and possible injuries.

Conclusion

Thus, neurological symptoms appeared as the patient voluntarily discontinued treatment for polycythemia vera. As a result of neurological examination the comorbid condition – CANVAS syndrome was revealed. The two diagnoses are not directly related to each other, but they can affect the course of another condition and thereby worsen the patient's quality of life. The clinical diversity of PV symptoms, the change in the size of the spleen, the duration of the course of the disease emphasize the need for prolonged dynamic observation of the given group of patients. Patients with changes in the complete blood count represented by the high level of red blood cells, hemoglobin, leukocytes, platelets require regular dynamic laboratory diagnosis as well as the control of drug administration to prevent disease progression, the development of complications and aggravation of comorbid conditions.

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