GENETICS, PROTEOMICS AND METABOLOMICS

GENETIC PRION DISEASE – FATAL FAMILIAL INSOMNIA (CLINICAL CASE)

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ABSTRACT

Background. *Fatal familial insomnia is a rare genetically determined neurodegenerative disorder from the group of prion diseases. Its main cause is the autosomal dominant D178N mutation of the PRNP gene, which leads to the synthesis of the pathological prion protein PrP.*
The aim. *Using the example of a clinical case to describe an example of the early onset of fatal familial insomnia in a teenager, a clinical example of its management.*
Materials and methods. *Female patient V., 16 years old, of hyposthenic constitution, undernourished, with negative family history (multiple sclerosis in her paternal grandmother) for the first time consulted a neurologist in Tver for the complaints of superficial sleep, shortened to 4–5 hours, unspecific pain all over the body, periodic numbness in the upper limbs. Six months later, retardation of speech and movements, changes in gait, and intentional tremor occurred; sleep was shortened to 2 hours. In the future, the teenager lost the ability to independently maintain the vertical body position, the ability to walk without assistance, speech was reduced to syllable answers to questions. In order to verify the diagnosis and to carry out differential diagnosis with other neurodegenerative diseases, the girl underwent auxiliary research methods: detection of antibodies to nuclear antigens, magnetic resonance imaging, computer electroencephalography, polyexomal genome sequencing.*
Results. *Based on the anamnesis, complaints, clinical picture and results of genetic research the final diagnosis of fatal familial insomnia was made. Due to the lack of etiological and pathogenetic therapy, the patient was subsequently provided with palliative medical care. The fatal outcome occurred 19 months after the onset of the disease.*
Conclusions. *The presented clinical case reflects the complexity of managing patients with rare genetic diseases, confirms the need for mandatory polyexomal genome sequencing in order to verify the diagnosis, which allows timely palliative care.*

Key words: *fatal familial insomnia, prion diseases, prion proteins, neurodegeneration*

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ГЕНЕТИЧЕСКОЕ ПРИОННОЕ ЗАБОЛЕВАНИЕ – ФАТАЛЬНАЯ СЕМЕЙНАЯ БЕССОННИЦА (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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РЕЗЮМЕ

Обоснование. *Фатальная семейная бессонница – редкое генетически детерминированное нейродегенеративное расстройство из группы прионных заболеваний. Основной причиной его возникновения является аутосомно-доминантная мутация D178N гена PRNP, приводящая к синтезу патологического прионного белка PrP.*

Цель. *На примере клинического случая описать пример раннего дебюта фатальной семейной бессонницы у подростка, клинический пример его ведения.*

Материалы и методы. *Пациентка В., 16 лет, гипостенического телосложения, пониженного питания, с отягощённой наследственностью (у бабушки по линии отца – рассеянный склероз) впервые обратилась к неврологу г. Тверь с жалобами на поверхностный, укороченный до 4–5 часов сон, боли неспецифического характера во всём теле, периодические онемения в верхних конечностях. Спустя полгода присоединились заторможенность в речи и движениях, изменение походки, интенционный тремор, сон укорочен до 2 часов. В дальнейшем подросток утратил способность к самостоятельному поддержанию вертикального положения тела, способность ходить без посторонней помощи, речь была сведена к односложным ответам на вопросы. С целью верификации диагноза и дифференциальной диагностики с иными формами нейродегенеративных заболеваний подростку проводились вспомогательные методы исследования: определение наличия антител к ядерным антигенам, магнитно-резонансная томография, компьютерная электроэнцефалография, полиэкзомное секвенирование генома.*

Результаты. *Учитывая анамнез, жалобы подростка, многообразие клинических проявлений заболевания, а также результаты полиэкзомного секвенирования генома, был поставлен окончательный диагноз фатальной семейной бессонницы. Ввиду отсутствия этиологической и патогенетической терапии больной в дальнейшем оказывалась паллиативная медицинская помощь. Летальный исход наступил через 19 месяцев после дебюта заболевания.*

Выводы. *Рассмотренный клинический случай отражает сложность ведения пациентов с редкими генетическими заболеваниями, подтверждает необходимость обязательного проведения полиэкзомного секвенирования генома с целью верификации диагноза, что позволяет своевременно оказывать паллиативную помощь.*

Ключевые слова: *фатальная семейная бессонница, прионнные заболевания, белки-прионы, нейродегенерация*

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BACKGROUND

Prion diseases are a group of neurodegenerative diseases that result from the conversion of the normal prion protein PrPC, which has a predominantly α-helical structure, into an abnormal form of the protein called the PrPSc prion. This group of human diseases occurs in most developed countries of the world with a frequency of 1–1.5 cases per 1 million per year. Among them, fatal familial insomnia with an autosomal dominant type of inheritance is distinguished, associated with a mutation in codon 178 (D178N) of the *PRNP* gene, located on the short (p) arm of chromosome 20 at position p13 [1]. As a result of missense mutation, normal aspartic acid (Asp) is replaced by asparagine (Asn), which leads to neuronal degradation, proliferation of astrocytes and microglial cells, accumulation of abnormal prion protein mainly in the anterior ventral and mediodorsal thalamus nuclei, inferior olivary nucleus, cerebellum and entorhinal brain cortex [2, 3]. Patients with fatal familial insomnia are more common in the age group from 20 to 61 years, and it is equally common among men and women. The fundamental symptom of this pathology is insomnia, and its severity correlates with the disease progression. Vegetative dysfunction may manifest itself in attacks of high blood pressure, episodes of tachypnea, hyperhidrosis, sexual dysfunction, and persistent subfebrile body temperature. In terms of the motor system, the most common are gait ataxia and myoclonus. In the area of cognitive impairment, inhibition, decreased concentration, and loss of short-term memory are prevalent. Dysarthria and bulbar dysfunctions may appear at a later stage. As the neurological deficit increases, changes in mental status are added [4, 5].

The complexity of managing patients with fatal familial insomnia is associated with the absence of specific signs of the disease in routine diagnostic methods, international standards of clinical diagnostic criteria, and the insufficient scientific data for the development of etiological and pathogenetic therapy [6, 7].

THE AIM OF THE STUDY

To describe an example of the early onset of fatal familial insomnia in an adolescent, and a clinical case of its management.

MATERIALS AND METHODS

Female patient V., 16 years old, of hyposthenic constitution, undernourished, hereditary tainted (multiple sclerosis in her paternal grandmother) for the first time consulted a neurologist in Tver in March 2019 for the complaints of sleep disorders, periodic numbness in the upper limbs, persistent dry cough, non-specific pain all over the body. It is known from the anamnesis that the first symptoms appeared in January 2019. According to the mother, against the background of a stressful situation in the family, the adolescent's sleep duration shortened to 4–5 hours, and parasomnias associated with the REM sleep, such as nightmares and dysphoria appeared. By the end of February, the patient began to complain of sensory disturbances, manifested by episodes of numbness in the upper limbs, non-specific pain all over the body, not related to physical activity, stress, or medication, and an obsessive dry cough.

Upon examination, the patient is hyposthenic, undernourished, skin and visible mucous membranes are of physiological color and moderate humidity. Vesicular breathing occurs in all parts of the lungs. Heart sounds are clear and rhythmic. Blood pressure is 110/75 mm Hg. Pulse is symmetrical, rhythmic, of satisfactory filling and tension, 96 beats per minute. The musculoskeletal system is normal. Urination and stool are not impaired. Neurological status: in the cranial nerves – horizontal nystagmus in extreme leads. Muscle tone is slightly reduced in the upper limbs. Tendon reflexes are brisk. In the Romberg pose, there is mild static ataxia.

Neurometabolic therapy (gamma-amino-beta-phenylbutyric acid hydrochloride 250 mg) and intramuscular injections of a vitamin complex containing thiamine disulfide, pyridoxine hydrochloride, and cyanocobalamin were prescribed.

In March, the patient was admitted to the neurology department of the regional hospital to clarify the diagnosis and treatment. The previously described symptom complex is joined by non-specific, constant pain in the back of the neck, non-systemic dizziness, and persistent increase in body temperature to 37.5 °C. Magnetic resonance imaging (MRI) with a power of 1.5 T did not reveal any pathology of the brain. Examination for systemic diseases showed the presence of antibodies to nuclear antigens – 0.2 units (with the norm being 0 units); other indicators were normal. A decision was made to continue the course of neurometabolic therapy in combination with therapeutic exercise and magnetic therapy for the neck area. A consultation with a psychotherapist was conducted and the presence of a depressive disorder was diagnosed; an antidepressant (escitalopram oxalate 5 mg) was added to the treatment regimen – showing no positive clinical effect. The neurologist transferred the patient to a tranquilizer (medazepam 10 mg) and a nootropic (hopantenic acid 250 mg), but the condition remained without positive dynamics.

Five months after the onset of the disease, the adolescent's sleep was shortened to 2 hours; speech and movement retardation, changes in gait such as obsessive short stepping movements when stopping, and intention tremor were observed. A second course of medazepam (15 mg) was prescribed, which led to sleep extension to 12 hours, but upon awakening, an attack of derealization occurred: the child did not understand where she was, what day and time it was, did not recognize the surrounding environment and spoke

phrases unrelated to the environment. The neurological status includes rest and action tremor (ability to walk independently is preserved), eyelid tics, ataxia, noisy sighs and vocalizations, diplopia, poor speech, mainly monosyllabic sentences. All therapy was discontinued. The patient was referred for a psychiatrist consultation, and borderline state of dissociative personality disorder was diagnosed. Neuroleptic treatment was prescribed – quetiapine fumarate 25 mg.

Six months after the onset of the disease, clinical manifestations are supplemented by obsessive head movements, non-specific pain in the lumbar region, and acute urinary retention. The patient was hospitalized, a second MRI scan with intravenous contrast was performed, but no specific data was found to determine the cause of the disease. The patient was diagnosed with undifferentiated hereditary degenerative disease of the central nervous system. During the patient's inpatient treatment, an episode of confusion was noted, symptoms of acute psychosis with attacks of depersonalization and derealization, autoaggression, chaotic movements, echolalia, and lack of insight into her condition appeared. Psychocorrection was carried out without pharmacological support. Discharged home for outpatient supervision.

In September 2019, the child's condition worsened: the patient lost weight to 47 kg, pelvic disorders in the form of daytime and nighttime enuresis, encopresis appeared. Due to progressive degenerative symptoms, she was referred to the neurology department of a federal hospital. There are medium-swinging horizontal nystagmus in extreme abductions in the area of cranial innervation. Positive symptoms of oral automatism (proboscis and nasolabial). In the motor-reflex sphere: impaired gait, astasia-abasia, the patient walks only with support, moves in small steps, during examination involuntarily moves the upper and lower limbs. Notable muscle hypotrophy is observed. Muscle strength is reduced in the lower limbs to 4 points. Muscle tone is altered according to the plastic type, the "cogwheel" symptom is noted in the upper limbs. Tendon reflexes from the upper limbs are high, with expansion of zones without a clear difference between the sides, from the lower limbs – are not evoked. Inconstant Babinski's symptom on the right. The patient does not manage to stand in the Romberg pose, sits with support. Intention on both sides during the finger-hammer test. There are pelvic organ dysfunctions in the form of periodic urinary retention and incontinence, constipation. Hyperhidrosis is observed, facial expression is poor, the patient answers questions passively, the answers are scanty. Speech is quiet, hyperlalia with a nasal tint. Pharmacological therapy was prescribed, including a multivitamin complex, valproic acid (300 mg), levocarnitine (1 ml), phenobarbital (25 mg). Discharged for residential treatment.

Twelve months after the onset of the disease, the child's condition remained severe. The patient's weight was 35 kg, body mass index was 14 kg/m^2. Upon examination: consciousness was confused, a forced position in bed was noted, accompanied by obsessive, fanciful movements of the limbs and trunk. The skin was pale gray, clean, there were periorbital dark circles on the face. Speech was still impaired, the patient answered questions with difficulty, used monosyllabic sentences. General hyperhidrosis with accompanying distal hyperthermia was observed. She could not sit or walk independently, movement was possible only with support. Pelvic organ functions were also impaired: stool with a tendency to constipation, dysuric phenomena in the form of urinary retention.

To verify the diagnosis, the patient underwent diagnostic tests. Thus, electroencephalographic monitoring showed slow forms of theta-range activity of 6 Hz, registered in all parts of the cerebral hemispheres, without regional differences.

General blood and urine analysis revealed no pathology. Polyexome genome sequencing revealed a mutation in the second exon of the *PRNP* gene, leading to the pAsp178Asn substitution, associated with fatal familial insomnia.

RESULTS AND DISCUSSION

Taking into account the anamnesis, complaints of the adolescent, the diversity of clinical manifestations of the disease, as well as the results of polyexome genome sequencing, the final diagnosis was: fatal familial insomnia. Due to the lack of etiological and pathogenetic therapy for this disease, the patient subsequently received palliative medical care. The fatal outcome occurred 19 months after the onset of the disease.

According to literature data, patients with fatal familial insomnia are more common in the age group from 20 to 61 years, and life expectancy varies from 7 to 72 months [8]. In the described clinical case, the onset was diagnosed in a 16-year-old girl; patients with fatal familial insomnia in adolescence have not been previously reported.

The presented clinical case demonstrates the ambiguity and multifaceted nature of clinical manifestations of fatal familial insomnia, which confirms the need to use unified diagnostic criteria. Thus, a clear diagnostic hierarchy was established, which included: organic symptoms associated with sleep in the form of intractable insomnia; decreased cognitive abilities in the form of progressive dementia; the appearance of hallucinations, delusional disorders, depression; dissociative identity disorder; weight loss of more than 10 kg over the past 6 months. The determining diagnostic criteria remained a positive family history with existing insomnia and data genome from polyexome sequencing with the identified mutation of the PRNP gene [9].

CONCLUSION

The clinical case reflects the complexity of managing patients with rare genetic diseases, in particular

with fatal familial insomnia, associated with the absence of specific changes during typical diagnostic procedures (MRI, EEG) and standards of etiopathogenetic therapy, which confirms the need for mandatory polyexome genome sequencing and detection of the D178N mutation to verify the diagnosis, allowing timely provision of palliative care.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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