GENETIC CHARACTERISTIC AND CLINICAL FEATURES OF CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL)

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Abstract

Introduction. *Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is one of the most common genetic causes of small-vessel cerebral diseases.*

Objective. *The aim of our study was to examine the frequency and severity of phenotypic spectrum in patients with CADASIL, including the study of the prevalence of the NOTCH3 gene mutations in patients with suspected CADASIL.*

Material and methods. *Sanger sequencing of exons 2–7, 11 of NOTCH3 gene was conducted in 314 patients with suspected CADASIL (confirmed by anamnesis and magnetic resonance imaging MRI). Clinical and MRI data were collected and analyzed for 14 patients with CADASIL.*

Results. *NOTCH3 gene aberrations in exons 2–7, 11 were detected in 34 of 314 examined patients, that is 11% of all cases. The most frequent aberrations are localized in exon 4 (70.4%), exon 3 and exon 6 (8.8%) of the NOTCH3 gene. A detailed analysis of clinical and instrumental data was conducted in 14 cases of confirmed CADASIL with pathogenic mutations.*

Conclusion. *The age of manifestation of CADASIL in the Russian population varies significantly. Patients without a previous history of TIA/stroke may have an atypical course of the disease, including cerebellar ataxia and epilepsy. MRI pattern of the CADASIL patients of the studied cohort showed no severe damage of external capsules and temporal lobes. Spinal cord lesion are not to be excluded as a CADASIL symptom.*

K e y w o r d s : CADASIL, *NOTCH3* gene, lacunar stroke, vascular dementia, brain, cervical spinal lesion

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Introduction. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is one the most common hereditary causes of an early stroke and small cerebral vessels disease [1]. The first case of CADASIL was, probably, described in 1955 by neurologist van Bogart, who observed a familial case of a rapidly progressing Binswanger's encephalopathy in middle-aged adults and concomitant neurological focal symptoms. Later, other clinical cases similar to the first one were described with the presence of ischemic strokes and a multifocal lesion of the white matter of the brain in the absence of typical vascular risk factors. *NOTCH3* gene was mapped in 1993, and three years later, taking into account genetic, clinical, and instrumental data, the neurological syndrome due to mutations in the *NOTCH3* gene was proposed to be designated as CADASIL. The prevalence of CADASIL was estimated between 2 to 4 cases per 100,000 individuals [2], however, some authors have shown, that the prevalence of CADASIL mutations can reach 5–10 cases per 1000 people in the population [3].

CADASIL is caused by a mutation in the *NOTCH3* gene on chromosome 19p13. *NOTCH3* gene has 33 exons, in which more than 200 different aberrations have been described. CADASIL is an autosomal dominant disorder and in 98% of cases results from point mutations of nucleotides in 2–24 exons of the *NOTCH3* gene, encoding extracellular EGF-like domains of the *NOTCH3* receptor. Nucleotide polymorphisms have often been found in exons 2–6 of the *NOTCH3* gene. It should be noted, that the analysis of the remaining exons 25–33 (which don't encode EGF-like domains) at the moment has not clinical significance, since the question of whether the changes in the amino acid sequence detected in this region are genetic polymorphisms or whether they are responsible for the development of CADASIL remains open [4].

CADASIL has characteristic manifestations, which are: migraine with or without aura, lacunar ischemic strokes, cognitive disorders, and mental disorders. However, the combination of all signs at the initial stage is rarely observed in patients, and sometimes atypical symptoms may dominate in the clinical picture of the disease [5].

The age of manifestation of CADASIL also may vary significantly: on average, the disease debuts at 30–40 years of age. Although cases of both late and early onsets of the disease are described [6, 7]. The rate of progression, severity, and prognosis of CADASIL depends on the localization of the aberration. Particularly, a consistent pattern has been demonstrated, that in people with pathogenic variants in 1–6 EGF-like domains stroke occurs 12 years earlier compared to patients, in whom a change in the number of cysteine molecules occurred in 7–34 EGF-like domains [8]. However, comorbid factors can also significantly change the course of the disease. Multifocal plaques in the brain, detected by MRI, may have similarities with the MRI of demyelinating diseases, including multiple sclerosis (MS), hereditary syndromes (Fabry's disease, MELAS), and other micro-angiopathies (Binswanger's disease), which significantly complicates the differential diagnosis of CADASIL.

The article is devoted to the study of frequency and severity of CADASIL in patients with a confirmed mutation of the *NOTCH3* gene and prevalence of *NOTCH3* mutations in patients with suspected CADASIL.

Material and methods. The study includes 314 patients. The study was approved by the local independent Ethical Committee of the Pavlov First Saint Petersburg State Medical University. All participants signed a voluntary informed consent to participate in the study.

A molecular genetic study was conducted in 314 patients with suspected CADASIL to detect changes in the *NOTCH3* gene. The criteria for inclusion in the study were the presence of migraine attacks and/or early ACVA (Acute Cerebrovascular Accident) before the age of 50, and/or a picture of a multifocal or diffuse pattern of plaques on the MRI of the brain.

Genomic DNA was isolated from peripheral blood leukocytes using QIAamp® DNA MiniKit according to standard protocol [9].

The molecular genetic study for the presence of nucleotide substitution in the *NOTCH3* gene (2–7, 11 exons) was carried out by direct automatic sequencing using Big Dye Terminator v3.1 Cycle Sequencing reagents from Thermo Fisher Scientific (USA) and the ABI 3500 genetic analyzer (Applied Biosystems, USA) following the manufacturer's instructions. The study didn't use direct sequencing of all exons encoding extracellular EGFR domains, because the frequency of pathogenic aberrations associated with CADASIL syndrome is the highest in exons 2–7, as well as in exon 11 according to A. Federico et al. [10].

The modified sequence of primers, used for amplification of the corresponding exons, and the conditions of the PCR reaction were previously published in the works of other researchers [11, 12].

Data from clinical, instrumental and neuroimaging studies were collected in 14 patients.

When analyzing the clinical picture, the following parameters were taken into account: family history, age of onset of the disease, the presence of such neurological features as migraine, transient ischemic attacks (TIA)/ischemic stroke, cognitive disorders, vertigo, atypical symptoms for CADASIL, if any.

The criteria for the classical manifestation of the disease are established by other authors in previously published works [1, 7].

The presence of cerebrovascular events in the form of migraines and/or early ACVA in the closest relatives of the 1st degree of kinship (according to the examined patients) was considered as a positive family history. Cases of CADASIL with a negative family history (including lack of information) are classified as sporadic.

The diagnosis of migraine was established by the criteria of ICHD-3 [13].

The presence of neurocognitive dysfunction, as well as mental disorders, was determined using the DSM-5 criteria [14]. The degree of cognitive decline was determined by the MoCA scale [15].

The MRI scans were evaluated using the neuroimaging criteria STRIVE (STandards for ReportIng Vascular changes on nEuroimaging), taking into account recent small subcortical infarcts, lacunae, hyperintensity of white matter, enlarged perivascular spaces, brain atrophy [16]. All MRI studies were performed on a tomograph with a magnetic field induction force of 1.5 Tesla in the 3D. T1-weighted sequence, 2D T2-weighted sequence, T2*-weighted GRE, DWI, FLAIR, modes images of the brain in the axial, sagittal, and coronal planes and of the spinal cord in the sagittal and axial planes were obtained.

The degree of severity and pattern of the focal lesion (foci of hypertensive signal in the white matter of the brain in the FLAIR mode) were evaluated using the Fazekas visual scale in the FLAIR mode: 0 — no foci; 1 — single foci; 2 — numerous discrete foci, sometimes they can merge; 3 — multiple confluent foci [17].

Statistical analysis of the results was performed using the GraphPad Prism 9 program. The comparison of quantitative data was carried out using the exact Fisher criterion.

Results. *Genetic study.* Mutations in 2–7, 11 exons of the *NOTCH3* gene in studied group were detected in 34 cases (11%).

Clinical and instrumental data were collected for 14 patients out of 34.

Statistically significant differences in the frequency of CADASIL in men and women were not found. Mutations in *NOTCH3* gene was detected in 10 out of 118 (8.4%) men and 24 out of 196 (12.2%) women, who entered the study ($p = 0.35$).

The distribution of identified mutations in the study is 10/34 (29.4%) in men, and 24/34 (70.6%) in women.

The hereditary nature of CADASIL is confirmed by a family with a positive family history in a number of generations, proven by migraine, ONMC, as well as an aberration in the *NOTCH3* gene (Table 1 and Table 2).

Mutations in exon 4 of the *NOTCH3* gene were detected in 24 cases (70.4%), in exon 3 — in 3 cases (8.8%). Mutations in the 2, 5, 7, and 11 exons were detected in isolated cases (3% each) (Fig. 1).

Demographic and neurological status. The data of anamnesis, neurological status, and instrumental findings were analyzed in 14 patients with CADASIL (the results are shown in Table 1 and Table 2). The median age of the disease onset was 32 [20; 37] years.

The 50% of patients suffered from a typical manifestation of CADASIL, which includes migraine or stroke. The manifestation occurred after they were 30.

The early manifestation of the disease before 30 years was observed in 6/14 patients (43%), among whom the vast majority had migraines with various types of aura.

Late debut (after 50 years) was detected in 1 patient, manifested by neurocognitive symptoms: memory loss and motor aphasia.

The manifestation of CADASIL with migraine headache developed in 8/14 patients (57%). The average age of onset is 24. Subsequently, 6 out of 8 patients with a migraine developed TIA or a cerebral infarction. In general, the diagnosis of "migraine with aura" was established in 7 patients (50%), and the main types of aura were visual, brainstem, or aphatic. Migraine without aura was recorded only in 3/14 patients (21%).

The manifestation in the form of a stroke was recorded in 5/14 (36%) patients. It occurred in the typical age range, accepted for CADASIL — 30–40 years in all cases. The leading clinical manifestation of CADASIL

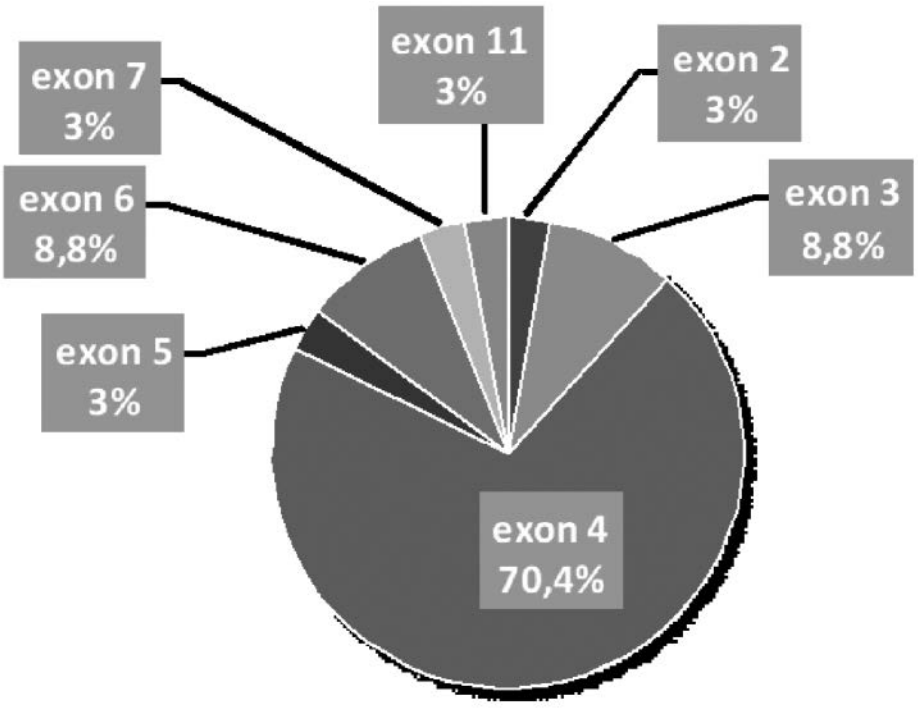

Fig. 1. Distribution of aberrations (amino acid sequence substitutions) by exons in 34 patients with identified mutations in the *NOTCH3* gene

in 12 (86%) patients was ischemic disorders of the brain in the form of TIA/ischaemic stroke. In 6 patients there were repeated ACVA. The main manifestation of a stroke in 9 patients (64%) was spastic hemiparesis. Cerebellar ataxia was detected in 6/14 patients (43%), and lesions of the cerebellum on MRI were found in 3/14 cases 21%. The frequency of hemihypesthesia was also 43%.

According to the results of neuropsychological testing, including the MoCA scale, mild and moderate cognitive impairment was observed in 6 patients, respectively (score below 27). The diagnosis of dementia was also made in 3 patients (21%), who scored below 16 on the MoCA score.

Vertigo of a systemic or non-systemic nature was noted in 9/14 patients (64%), and in 6 patients (43%) vertigo was not associated with migraine headache attacks.

Various mental disorders were identified in 6 patients (43%), the main clinical variants of which were cyclothymia, depression, and bipolar disorder. The patients also had cases of anxiety and apathy.

Disorders of higher cortical functions were observed in 2 patients (14%), more often manifested by sensorimotor aphasia and finger agnosia.

Partial epileptic seizures were recorded in two patients: in one patient in the form of affective paroxysms with the addition of unmotivated aggression, and the other — in the form of focal motor epilepsy.

Diseases, associated with CADASIL. Cardiovascular symptoms were detected in 4 patients and manifested mainly in the form of sinus node dysfunction, right bundle branch block, diastolic dysfunction of the left ventricle.

Retinal angiopathy was also detected in 5 patients (36%). The angiopathy was not associated with hypertension in 2 patients.

Neuroimaging in CADASIL. The MRI of the examined patients showed a characteristic pattern. The involvement of anterior and temporal lobes and external capsules was observed in 8 patients (57%). Either temporal lobe or external capsules were involved in 2 patients. White matters hyperintensities were evaluated using the Fazekas scale. The first degree of changes was detected in 2 patients (14%), the second degree — in 6, the third degree — in 6 patients (43%, respectively).

Lacunar infarcts were detected in 64% of patients, which were mainly located in the area of the basal ganglia and the pons. Lacunae in the cerebellum were detected only in 3 patients. Moderate and pronounced atrophic changes of the brain were observed in 5 patients, which accounted for 36% of cases of the disease. The

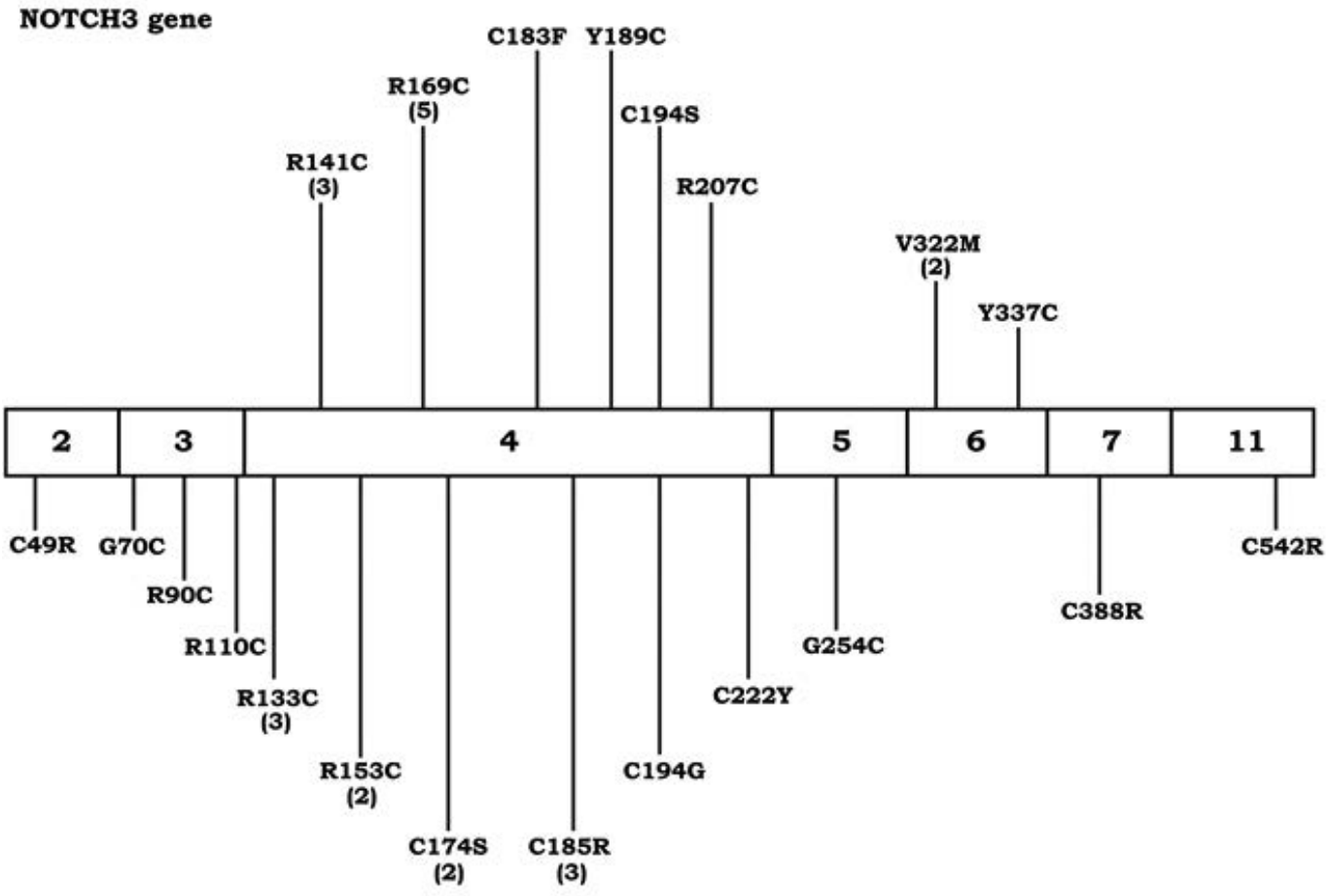

Fig. 2. The structure of the *NOTCH3* gene and localization of mutations by exons.
Note. The number of people with specific changes in the genetic code is indicated in parentheses, if there was more than one of them

Table 1

Anamnesis of patients with a mutation of the *NOTCH3* gene

Patient	Sex/age	Aberration/ exon	Family history	Manifestation of disease, age/syndrome	Ischaemic strokes (IS)/ TIA, number	Other disease
1	M/36	p.R133C (4)	+	33/ stroke	IS-1; TIA-1	2; 3
2	F/32	p.R141C (4)	+	29/migraine	IS-2; TIA-1	1
3	M/47	p.R169C (4)	+	39/stroke	IS-2; TIA-0	–
4	F/46	p.C174S (4)	+	41/stroke	IS-2; TIA-0	–
5	F/47	p.R169C (4)	–	36/stroke	IS-3; TIA-0	–
6	F/24	p.C542R (11)	–	20/migraine	–	–
7	F/51	p.R169C (4)	+	25/migraine	IS-1; TIA-0	1; 3
8	M/40	p.C185R (4)	+	37/stroke	IS-3; TIA-3	1; 2; 3
8.1	M/39	p.C185R (4)	+	35/migraine*	–	–
9	F/59	p.C185R (4)	+	15/migraine	IS-1; TIA-0	1
10	M/39	p.C388R (7)	–	32/migraine	IS-1; TIA-0	2
11	F/34	p.R153C (4)	+	26/migraine	IS-1; TIA-0	3
12	F/60	p.C183F (4)	–	50/cognitive impairment	IS-3; TIA-0	1; 2; 3
13	F/36	p.G254C (5)	–	14/migraine	IS-0; TIA-2	–
	Total, *n* (%)		9 (64)	Under 30 years — 6 (43) After 50 years — 1 (7)	12 (86)	8 (57)

Note: 1 — hypertension; 2 — heart disease; 3 — retinal angiopathy. *Family cases: 8 and 8.1 — siblings. The sign "–" indicates the absence of a syndromes in the patient; *n* — the number of patients.

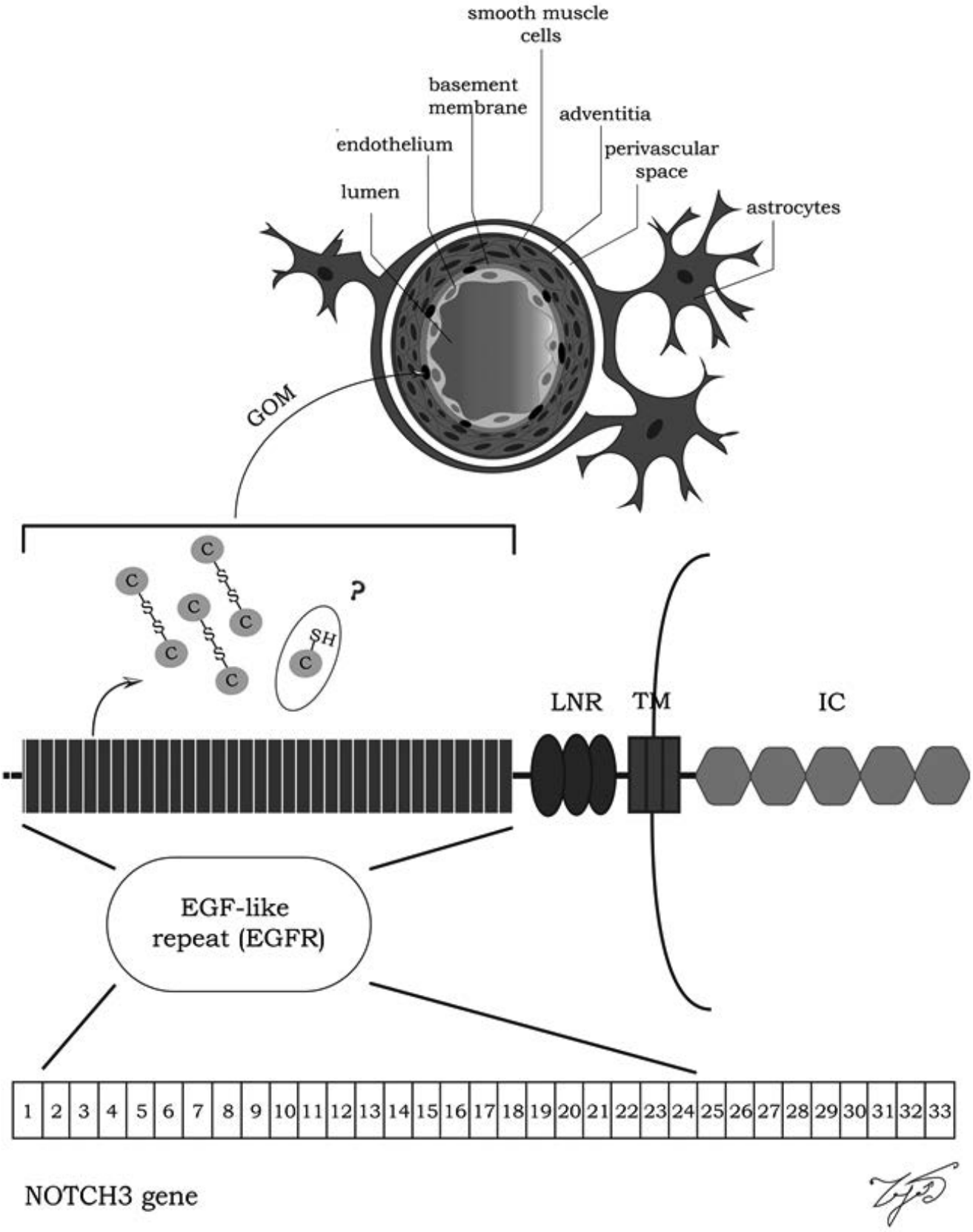

Fig. 3. Pathogenesis of vasculopathy in CADASIL. Genetic aberrations in 2–24 exons of the *NOTCH3* gene lead to the appearance of an odd number of cysteine molecules (indicated by an arrow in the figure) in the external domain of the *NOTCH3* receptor (EGFR). As a result, the tertiary structure of EGF-like domains changes, which are deposited in the basement membrane of blood vessels in the form of GOM (indicated by an arrow in the figure).
Note: EGFR — epidermal growth factor-like repeat; LNR — Lin12 repeats; TM — transmembrane domain; IC — intracellular domain; GOM — granular osmiophilic material

Table 2

Clinical features of patients with CADASIL mutations

Patient	Migreine/ aura (+/–)	Vertigo	MoCA, score	Disturbances of higher cerebral function	Psychiatric Illness	Seizures	Paresis	Neurostatus
1	+/–	+	27	–	+	–	–	1; 2
2	+/+	+	22	–	+	+	hemiparesis	1; 3
3	–	+	24	–	–	–	tetraparesis	4; 5
4	–	+	24	–	–	–	tetraparesis	1; 5
5	–	+	21	–	–	–	–	1; 3
6	+/–	+	24	–	–	+	–	–
7	+/+	+	29	–	+	–	hemiparesis	3; 4
8	+/+	+	14	–	+	–	tetraparesis	2; 3; 4; 5; 6; 7
8.1	+/+	–	28	–	–	–	–	–
9	+/+	–	6	–	+	–	hemiparesis	5; 6; 7
10	+/–	–	29	–	–	–	–	3
11	+/+	–	27	–	–	–	monoparesis	2; 3; 4
12	–	+	15	+	+	–	monoparesis	4; 5; 6; 7
13	+/+	–	21	+	–	–	hemiparesis	–
	10 (71%)	9 (64%)	22.21 ± 3.66	2 (14%)	6 (43%)	2 (14%)	9 (64%)	

Note: 1 — oculomotor disfunction; 2 — central facial palsy; 3 — hemihypesthesia; 4 — pseudobulbar palsy; 5 — cerebellar ataxia; 6 — extrapyramidal symptoms; 7 — urinary urgency. The sign "–" indicates the absence of a sign in the patient.

MRI of the cervical spine was performed in 5 patients. Cervical spinal cord was affected in one patient.

Discussion. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetically determined form of small vessel disease associated with central nervous system damage. CADASIL is caused by mutations in the *NOTCH3* gene.

Normally, each of the extracellular domains of the transmembrane receptor of the *NOTCH3* gene consists of an even number of cysteine molecules connected by disulfide bonds (Fig. 3). However, the emergence of mutations in the *NOTCH3* gene leads to: the loss or appearance of TGT or TGC codons, which encode the amino acid cysteine; violation of the spatial conformation of the external domain; protein aggregation and its accumulation in the basement membrane of vascular smooth muscle cells and pericytes of cerebral arteries and capillaries in the form of granular osmiophilic material (GOM) [18]. As a result, the function of the receptor is disrupted, which is believed to be involved in the processes of differentiation and maturation of vascular smooth muscle cells, as well as the transmission of signals to the nucleus and the activation of nuclear transcription factors. On the other hand, the accumulated GOM, which is resistant to degradation, may have toxic properties. It is noteworthy that with CADASIL, not only vascular smooth muscle cells and pericytes are affected, but also endothelial cells and astrocytes, which indirectly indicates a violation of the trophic tissues. In rare cases, patients are found to have genetic variants that do not change the number of cysteine molecules in the external domain, but their clinical significance remains unclear [4].

Genetic study. The data of genetic study are comparable with the study of H.S. Markus et al. This study includes the British cohort of patients. It showed that the frequency of clustering of missense mutations in exon 3 and exon 4 reached 81% [11].

Most of the mutations in this study were characterized by a change in the number of cysteine residues, but a p.V322M mutation with uncertain clinical significance was found in 2 patients. This mutation did not lead to a change in the number of cysteine molecules. The mutation p.V322M was detected and described in the Russian Federation in the work of S.N. Illarioshkin et al., where it was defined as pathogenic [1]. In the present study, its pathogenetic significance remained unknown due to the lack of detailed patient history.

Demographic and neurological status. One of the most common symptoms of the disease is migraine with aura, which debuts on average at the age of 30 years. The average age of the manifestation with migraine in this study was 24 years. Various phenotypic variants of migraine with aura were observed in 7 out of 14 (50%) patients, what compatible with the data from research conducted outside Russia [19].

Another typical presentation of CADASIL is considered to be TIA and brain infarction, which are represented by such lacunar syndromes as “pure motor deficit”, ataxic hemiparesis, “pure sensory deficit” and “sensory-motor deficit”. ACVA is a leading clinical manifestation of CADASIL in 12 patients in the examined group (86%), which is comparable to the global statistics of the frequency of ischemic events in CADASIL (60–85%) [18]. The main manifestation of a brain infarction in most cases was paresis of various types (64%). The most common objective neurological syndromes were hemihypesthesia, cerebellar ataxia, oculomotor disorders, and pseudobulbar syndrome, the frequency of which coincided with the data presented in other studies [5]. A distinctive feature of ischemic events in CADASIL is their recurrent nature, which corresponds to the data obtained in this study: single and repeated strokes occurred in 6 and 6 patients, respectively [19].

Cerebellar ataxia was registered in 6 patients (43%). That data corresponded to the study by M. Dichgans et al., in which symptoms of cerebellar dysfunction was detected in 37% of patients [5]. Lacunar infarcts in the cerebellum caused ataxia in 21% of patients and were detected via MRI.

Lacunar infarctions in the cerebellum were not detected in 21% (3/14) of other cases. Cases of cerebellar syndrome in patients with CADASIL without neuroimaging signs of cerebellar infarcts were described earlier by other researchers [20, 21]. The frequency of this phenomenon is unknown. However, C. Vedeler et al. described a family case of CADASIL, in which three out of four relatives had symptoms of progressive cerebellar dysfunction without corresponding abnormalities on MRI [21]. D.G. Park et al. suggested, that cerebellar ataxia may be the only initial symptom of CADASIL when the patient doesn’t have other typical signs [20]. A possible explanation to this is a progressive endothelial dysfunction, degeneration, and thickening of the vascular muscle membrane, followed by vascular tone dysregulation. A chronic cerebellar hypoperfusion develops as a result. This leads to cerebellar ataxia in the initial stage, but structural changes are not visualized when performing routine MRI protocols [20].

The impairment of the cognitive profile was confirmed in 43% of patients in the form of attention disorders and memory loss. Although according to several studies, cognitive dysfunction is observed with a frequency of up to 60% [22]. It is believed that repeated strokes lead to progressive vascular-type dementia, which was detected in 3 patients, while in 1 patient the disease began with cognitive dysfunction in the absence of migraine headaches and clinically recorded ACVA. White matters hyperintensities were detected at MRI of this patient, which may indicate that he suffered microinfarctions of the brain without obvious focal neurological manifestations, i.e. clinically asymptomatic, with signs of gradually and slowly progressing cortical-subcortical dysfunction, which reflects the relevance of the differential diagnosis of CADASIL with cognitive disorders of various genesis.

In the group of examined patients vertigo of a systemic and non-systemic nature was registered in 64% of patients. Vertigo was not associated with migraine headache attacks in 43% of patients, but is most likely observed either as an independent symptom of CADASIL

or as a result of lacunar infarcts in the cerebellum or damage to the temporal lobes of the brain. Some authors attribute vertigo to rare symptoms of CADASIL, others report a high frequency — up to 25%, which together with our data indicates the significance of this clinical manifestation in CADASIL [23].

Disturbances of other higher cortical functions are a rare symptom of the disease, the frequency of which is not exactly known [18]. 2 out of 14 examined patients showed signs of cortical dysfunction in the form of sensorimotor aphasia and finger agnosia. Subcortical infarctions of the brain probably led to cortical ischemia and necrosis of neurons in the frontal, temporal and parietal lobes of the dominant hemisphere of the brain.

One of the rare clinical manifestations of CADASIL is epileptic seizures, the prevalence of which reaches 10% [5]. Epilepsy mostly develops after a stroke. Epileptic seizures were observed in 2 out of 14 patients (14%) in the studied group. However, brain infarction was not recorded in the anamnesis of 1 patient, and lacunar infarctions were not also detected via MRI. Generalized and focal epileptic seizures without previous ischemic events in the anamnesis were earlier described in the work of J. Haan et al. [24]. The pathogenesis of epilepsy, in this case, is most likely associated with possible ischemic micro-injuries of neurons.

Diseases, associated with CADASIL. Currently, there are conflicting opinions about whether CADASIL causes damage to the cardiovascular system or not. We identified heart damage in 4 patients (28%), manifested mainly in the form of sinus node dysfunction, right bundle branch block or diastolic dysfunction of the left ventricle. Our results are consistent with the data of the study conducted by L. Oberstein et al., in which up to 25% of patients with CADASIL have a history of acute myocardial infarction or current pathological *Q* waves on the ECG according to her study [25].

5 patients (36%) had retinal angiopathy as an associated condition. It was also noted by other researchers who recorded narrowing of the artery lumen, an increase in the lumen of the veins, and a decrease in the density of the deep vascular plexus of the retina in patients with CADASIL [26].

Neuroimaging in CADASIL. 57% of patients had an involvement of the anterior parts of the temporal lobes and 57% of patients had an involvement of the external capsules. Although, according to the study of H.S. Markus et al., involvement of the poles of the temporal lobes and external capsules in the pathological process was observed in 89% and 93% of cases, respectively [11]. This difference can be explained by the clinical heterogeneity of CADASIL, individual features in patients in the Russian population and the age of patients with early manifestation of the disease and the duration of the disease. According to MRI, spinal cord lesion and oligoclonal bands in the cerebrospinal fluid were detected in one patient, which is more common in multiple sclerosis. There are also data on a patient with a mutation of the *NOTCH3* gene, foci in the spinal cord, and intrathecal synthesis of oligoclonal IgG in the study conducted by P. Bentley et al. Therefore, the question remains whether an inflammatory component can appear itself in CADASIL or the presented observations reflect variants of comorbidity and the development of a demyelinating process in a carrier of a mutation in the *NOTCH3* gene [27].

Conclusion. CADASIL is characterized by highly non-specific vascular symptoms, manifestations and MRI signs. The prevalence of CADASIL mutations in the examined patients is about 11% in exons 2–7, 11 of the *NOTCH3* gene. The most frequent mutations were located in exons 4 (70.4%), 3 and 6 (8.8% each). The number of sporadic cases is high (5/14; 36%). The age of CADASIL manifestation in Russian patients varies significantly, both the early manifestation of the disease with migraine and the late one with dementia are characteristic. It has been shown that patients may experience cerebellar ataxia and epilepsy without corresponding structural changes on standard MRI protocols, which may indirectly indicate the development of microischemia/microhemorrhages. It also may have a significant effect on neurons at the early stages of the disease and requires a more detailed examination. Typical MRI signs of the disease were not found in all the examined patients: only 57% of patients had an involvement of the anterior temporal lobes and 57% of patients had an involvement of the external capsules. It may indicate the appearance of these MRI patterns at a certain stage of the disease and possibly not in all patients with CADASIL. There was an involvement of the spinal cord detected via MRI in 1 CADASIL patient, which does not exclude his diagnosis, but requires further observation for possible associated demyelinating disease.

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