Hereditary Multiple Cerebral Cavernous Malformations Associated with Wilson Disease and Multiple Lipomatosis

Olga B. Belousova[1], Dmitry N. Okishev[1], Tatyana M. Ignatova[2], Maria S. Balashova[3], Eugenia S. Boulygina[4]

Key words
- Comorbidity
- Genetics
- Hereditary cerebral cavernous malformations
- Multiple subcutaneous lipomatosis
- Wilson disease

Abbreviations and Acronyms
CCM: Cerebral cavernous malformation
CNS: Central nervous system
MRI: Magnetic resonance imaging
SNP: Single nucleotide polymorphism

From the [1]Vascular Department, N. N. Burdenko National Center of Neurosurgery Under Ministry of Health of the Russian Federation, Moscow; [2]State Education Institution of Higher Professional Training, First Sechenov Moscow State Medical University Under Ministry of Health of the Russian Federation, Department of Therapy and Occupational Diseases, Moscow; [3]The State Education Institution of Higher Professional Training, First Sechenov Moscow State Medical University Under Ministry of Health of the Russian Federation, Chair of Medical Genetics, Moscow; and [4]National Research Centre "Kurchatov Institute", Moscow, Russian Federation

To whom correspondence should be addressed: Dmitry N. Okishev, M.D., Ph.D. [E-mail: okishev@neurovascular.ru]

Citation: World Neurosurg. (2017). http://dx.doi.org/10.1016/j.wneu.2017.06.002

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

We report on a patient with 2 Mendelian diseases—symptomatic multiple familial cerebral cavernous malformations (FCCMs) and Wilson disease. Genetic analysis revealed single nucleotide polymorphisms in genes *CCM2* and *CCM3*, associated with cavernous malformations, and homozygote mutation in the *ATP7B* gene, responsible for Wilson disease. FCCMs were symptomatic in 3 generations. The patient also had multiple lipomatosis, which is suggested to be a familial syndrome.

In recent years there has been an increasing amount of publications linking FCCMs with other pathology, predominantly with extracranial and intracranial mesenchymal anomalies.

The present study is the description of an unusual association between 2 independent hereditary diseases of confirmed genetic origin—a combination that has not been described previously.

INTRODUCTION

Cerebral cavernous malformations (CCMs) are well-known vascular malformations composed of tightly packed abnormal blood vessels that lack elastic membrane and muscle cells and form numerous cavities, filled with blood.[1,2] CCMs are most often manifested by epileptic seizures or acute/subacute development of focal neurologic deficit, caused by intracerebral hemorrhage.[2,3] CCMs may be sporadic or inherited. The latter have autosomal-dominant type of inheritance and are associated with mutations in so-called CCM genes: *KRIT1*, *MGC4607*, or *PDCD10*.[4,5]

Both sporadic and familial CCMs may coexist with other intracranial and extracranial vascular and nonvascular pathology. Such association seems to be more characteristic for familial cases of CCMs. According to publications, the most common is the association with various types of cutaneous angiomas[6-17] and such neurocutaneous syndromes as neurofibromatosis type I (NF1).[18] Several cases of coexistence with cerebral arteriovenous malformations, arterial aneurysms, and various intracranial tumors are described.[2,19,20] Extracranial pathology is represented by cavernous angiomas of retina.[21,22] In rare cases, CCMs are associated with orbital cavernous hemangioma,[23] atrial myxoma,[24,25] Birt-Hogg-Dube syndrome,[26] Klippel-Trenaunay Weber syndrome,[27] and cavernous malformations of extracranial locations.[28,29]

This paper presents a unique patient with multiple familial cerebral cavernous malformation, Wilson disease, and subcutaneous lipomatosis who was successfully treated in N. N. Burdenko National Center of Neurosurgery (N. N. Burdenko NCN) and the Department of Therapy and Occupational Diseases of I. M. Sechenov First Moscow State Medical University (I. M. Sechenov FMSMU).

CASE REPORT

History and Examination

A young female (patient K), born in 1972, was admitted to N. N. Burdenko NCN in September 2006. She had acute onset of the disease in 2002 with an episode of intensive headache and transient partial loss of vision. In 2006 she experienced unsteadiness, moderate headache, and recurrent partial vision loss. computed tomography and magnetic resonance imaging (MRI) of the head revealed obstructive hydrocephalus and typical multiple CCMs: midbrain cavernoma with signs of previous and subacute hemorrhages and typical cavernomas of right frontal and left temporal lobes (Figure 1A–C). On admission, she was confused and disoriented. Neurologic examination showed up-lateral right eye deviation, narrowed equal pupils with satisfactory pupillary light reflex, vertical gaze palsy, athetoid movements in the right hand, Babinski symptom on the right, and marked ataxic gait. Ophthalmic examination revealed prominent bilateral edema of optic nerve discs.

General Condition. Her body weight was 105 kg. She had multiple subcutaneous

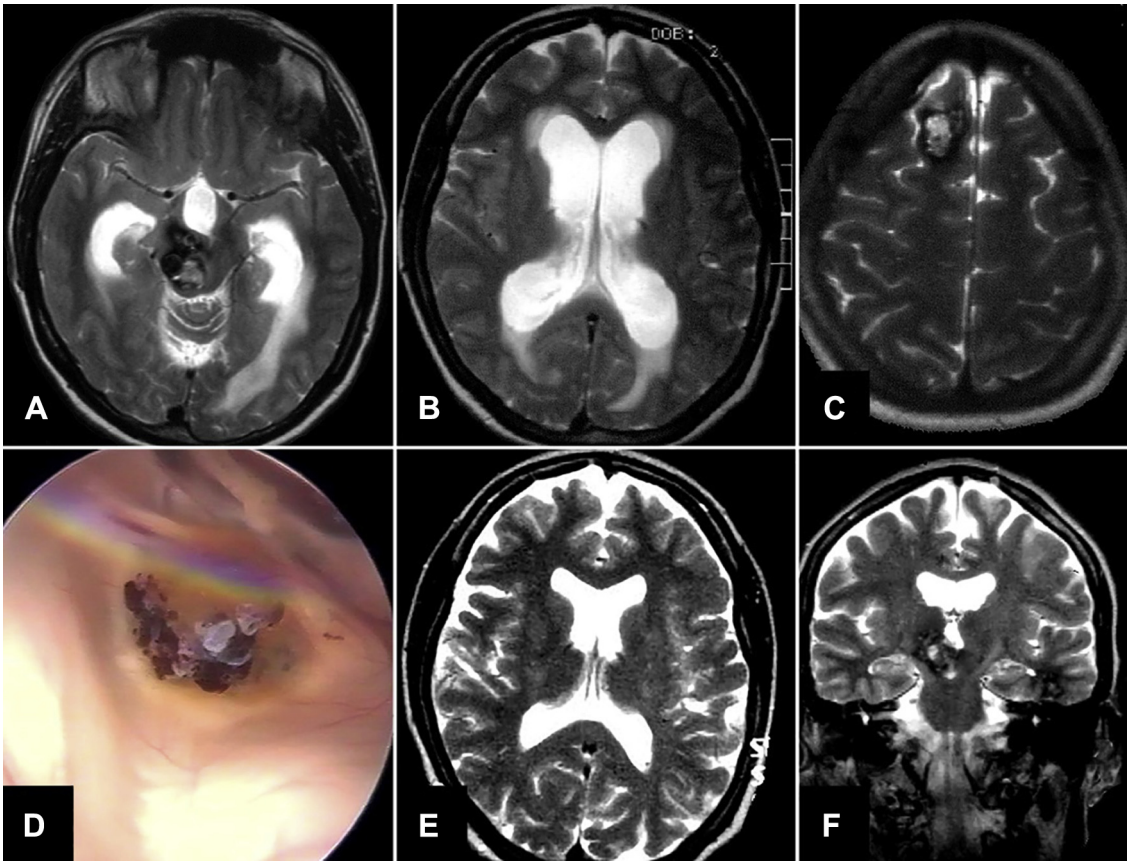

Figure 1. Patient K., proband. Multiple cerebral cavernous malformations (CCMs): midbrain cavernoma, penetrating into the III ventricle, typical cavernomas of right frontal and left temporal lobes. Midbrain cavernoma has signs of previous and subacute hemorrhages and causes obstructive hydrocephalus. (**A**–**C**) Magnetic resonance imaging (MRI) before operation, T2. (**D**) Endoscopic view of the third ventricle floor. CCM obturates the entrance to the aqueduct. (**E** and **F**) MRI after operation, T2.

lipomas in upper and low extremities and body, one of which, in the lumbar region, was surgically removed previously.

Management. Because of the location of the symptomatic cavernoma in a highly eloquent zone, mild local signs, and the prevalence of signs of obstructive hydrocephalus, the decision was made to restrict treatment to cerebrospinal fluid deviation by means of the third ventriculostomy. During the operation, the intraventricular subependymal portion of cavernoma was clearly seen (Figure 1D). The postoperative period was uneventful. Postoperative MRI showed regress of hydrocephalus (Figure 1E and F). The patient was discharged on the 7th day after the operation with marked clinical improvement and residual mild insufficiency of the right oculomotor nerve.

Follow-Up. Up to 2011 her course was uneventful. In 2011, she demonstrated yellowing of the sclera and fatigue. Examination in the clinic of the I. M. Sechenov FMSMU revealed jaundice, mild liver enlargement, moderate ascites, and leg edema. Blood samples showed hyperbilirubinemia (170 μmol/L) mainly due to indirect fraction (88 μmol/L) and anemia (hemoglobin—94 g/L) with negative Coomb test. Liver function tests demonstrated increased activity of aspartate transaminase, alanine transaminase, and gamma-glutamyl transpeptidase up to 130 ME, 83 ME, and 250 ME, respectively, and decreased levels of total protein (55 g/L) and albumin (26 g/L). She also had thrombocytopenia (89 × 109/L) and signs of liver cirrhosis in the samples of liver biopsy. Serum ceruloplasmin level was 16 mg/dL. Diagnosis of Wilson disease was confirmed by detection of a Kaiser-Fleisher ring and detection of homozygote gene mutation ATP7B c. 3207C>A. There were no typical neurologic symptoms or MRI abnormalities. Therapy with D-penicillamine 1500 mg/day was started. During the first year of treatment, all clinical signs disappeared and recovery of synthetic liver function and normalization of all blood tests were observed.

Follow-up investigation in May 2016 showed stable neurologic condition with mild mesencephalic signs, unchanged CCMs on MRI, and clinical and laboratory remission of Wilson disease. She received

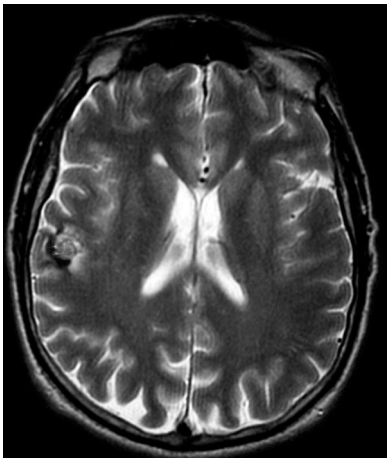

Figure 2. Patient P., proband's father. Cerebral cavernous malformation of the right frontal lobe. Magnetic resonance image before operation, T2.

treatment at the maintenance dose of D-penicillamine (750 mg/day). She returned to normal lifestyle and social activity.

Family History

The patient's father (patient P), born in 1947, experienced the series of epileptic seizures followed by right VII nerve palsy and speech disturbance in 2006. A MRI revealed right frontal lobe cavernoma (Figure 2). It was removed 2 weeks after manifestation. Histologic examination showed cavernous malformation. On follow-up, his condition remains normal. The patient's daughter (patient Sh.), born in 1999, had an episode of a sudden loss of consciousness in 2009. Brain MRI revealed a small lesion in the right frontal lobe, consistent with the diagnosis of cavernoma (Figure 3A and B). In December 2014 she had a sudden fall followed by nausea and headache for several days. MRI showed new lesion in right parietal lobe, highly consistent with the diagnosis of de novo cavernoma (Figure 3C and D).

Genetic Analysis of Family

The patient's parents are not involved in a consanguineous marriage and originate from different regions (Figure 4).

Genetic analysis was as follows:

1) An illumina sequencing test was used to diagnose Wilson disease. It revealed the homozygous mutation c.3207C>A (His1069Gln) in gene *ATP7B*, most frequent in the European population.
2) For familial CCMs, blood samples of the proband, her father, and her daughter were analyzed for the presence of large deletions/duplications by multiplex ligation-dependent probe amplification. No gross mutations in known CCM genes were found, so the whole genome sequencing was performed to search for single nucleotide mutations (SNPs). SNP analysis identified mutations in gene *MGC4607* (*CCM2*)—g.45078027T>C and SNP in gene *PDCD10* (*CCM3*) (synonymous names—rs116154329, c.150 G>A, or p.K50K), which can play a modifying role. No mutations were found in gene *KRIT1* (*CCM1*).

DISCUSSION

This case demonstrates a unique coexistence of 2 independent Mendelian diseases: hereditary CCMs, that have autosomal-dominant type of inheritance with the incomplete penetrance of the gene[30,31] and Wilson disease, which has the prevalence 1:30,000 and is inherited in

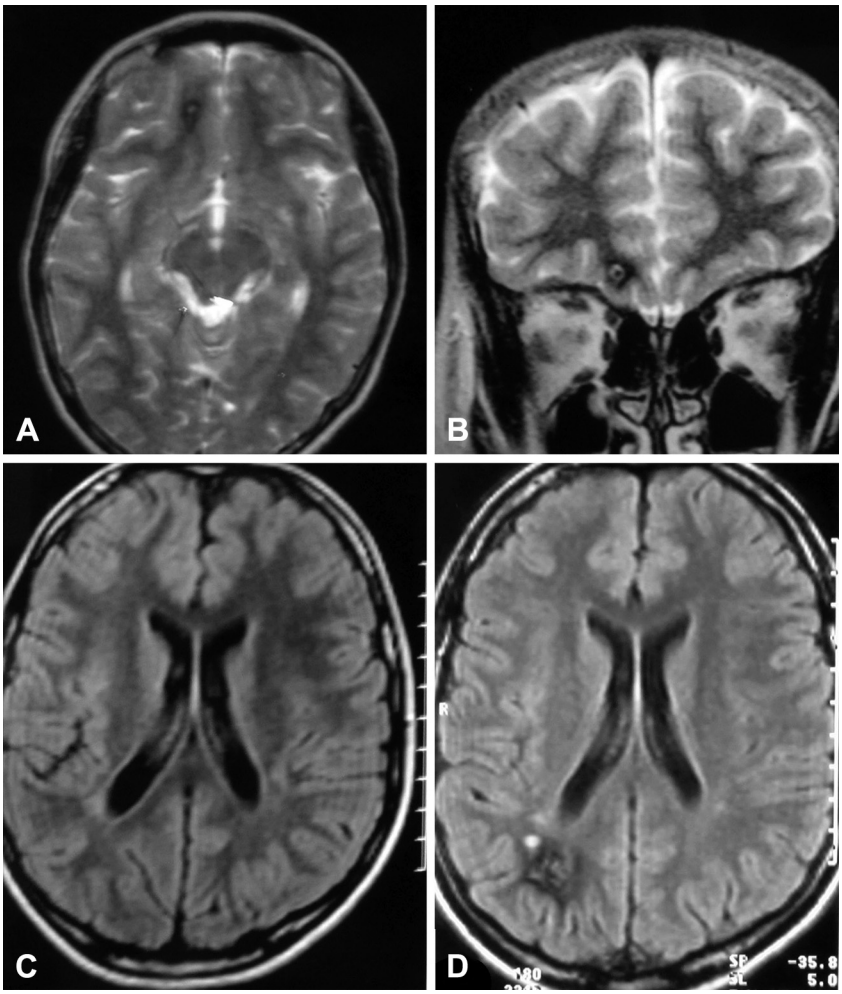

Figure 3. Patient Sh., proband's daughter. Multiple cerebral cavernous malformations (CCMs). (**A** and **B**) Magnetic resonance imaging (MRI) in 2009, T2. CCM of the right frontal lobe. (**C**) MRI in 2009, fluid-attenuated inversion recovery (FLAIR) (for comparison with **D**). No pathology is seen. (**D**) MRI 2014, FLAIR. De novo CCM in the right parietal lobe.

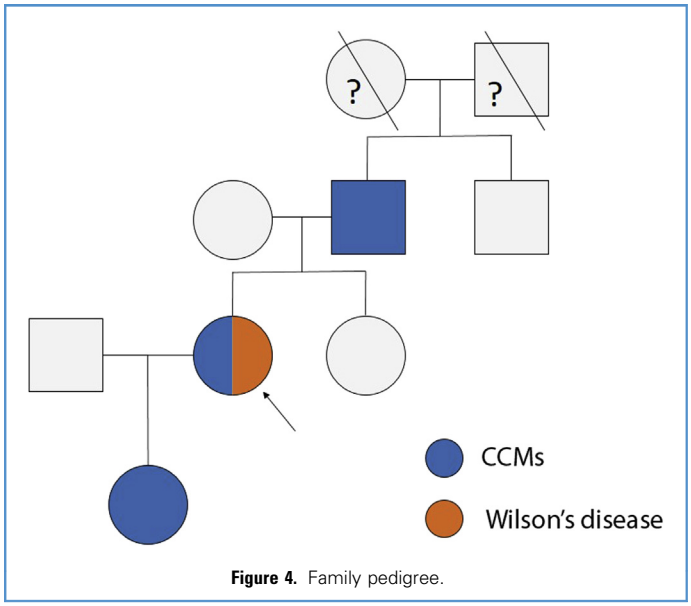

Figure 4. Family pedigree.

autosomal-recessive type.[32] It is also worth mentioning that the patient had multiple subcutaneous lipomatosis, which, according to several investigations, could be familial and may have a genetic nature.[33-35] There is also evidence of high prevalence of subcutaneous lipomas, mainly multiple, in patients with Wilson disease.[36]

It is worth emphasizing the following clinical features of this case: 1) the late onset of Wilson disease (at age 39 years) and its abdominal form with decompensated liver cirrhosis without neurologic manifestations and 2) earlier manifestation of CCMs in every next generation, typical for hereditary CCMs, and a de novo formation of cavernoma in the daughter of the proband.

Management of both diseases was effective. A permanent remission for >10 years confirms the low risk of hemorrhage from CCMs and supports the possibility of palliative surgery in cases of highly eloquent locations of the lesions. Anti-copper therapy allowed to change the unfavorable prognosis in a patient with decompensated liver function and cirrhosis.

Genetic analysis for both clinical conditions showed mutations in corresponding genes. For Wilson disease, typical homozygote mutation in gene ATP7B was revealed, which is most frequent for the European population.[37]

For CCMs, SNPs in 2 of the 3 known genes associated with this pathology were found: g.45078027T>C in *MGC4607* (*CCM2*), which, according to the literature, may lead to the formation of the donor site of splicing, and SNP rs116154329 in *PDCD10* (*CCM3*), the role of which is still unknown.[38-40]

The phenomenon of comorbidity is known for a number of diseases, including pathology of CNS. In a few studies the attempt is made to find the molecular genetic bases of comorbidity.[41,42] It was demonstrated that some genes, causing Mendelian disease, can contribute to the development of multifactorial pathology.[43,44] The prevalence of the coexistence of CCMs with other extracranial and intracranial pathology is unknown. In the series of approximately 2000 sporadic and hereditary CCMs treated in Burdenko NCN for the past 20 years, such association was analyzed for 1748 patients who underwent either an operation or alternative treatment. Widespread systemic diseases (arterial hypertension, atherosclerosis, inflammatory bronchopulmonary disease, diabetes type II, cancer, and others) were excluded. Patients with supposedly radio-induced CCMs were also excluded (11 cases). Associated pathology was found in 118 patients (6.7%). Several patients had >1 diseases; therefore the incidence of comorbidities was 7.2% (**Table 1**).

Data on 80 of these patients were published previously.[2] Data were evaluated retrospectively according to the history and results of the clinical examination. Special instrumental studies on the search for asymptomatic pathology were not conducted. We believe that with a careful prospective study, these figures would be higher. However, it is obvious that almost half of the pathology can be attributed to minor congenital disorders and malformations, both intracranial and extracranial.

The main question in all these combinations is the presence of genetic links between these types of pathology. Such links were demonstrated for cutaneous angiomas. Most frequently they were found in CCMs, associated with mutations in the *KRIT1* gene[12,45-47] but also in genes *CCM2*[16] and *CCM3*.[17] Campione et al[48] described the case of a woman with multiple cutaneous angiomas without cerebral CCMs and with a negative test for the *CCM1*, *CCM2*, and *CCM3* genes, but brain CCM was revealed in her daughter. Descriptions of CCMs also exist in patients with NF1, which is characterized by CNS tumors and pathology of skin, eye, cardiovascular, and cerebrovascular systems. The latter can manifest with aneurysms, arteriovenous malformations, CCMs, and moyamoya disease.[18,26,49] Ardeshiri et al[24] suggested possible existence of a common basis for brain CCMs and other mesenchymal pathology, by means of impaired differentiation of mesenchymal cells through common signaling pathways with CCM genes.[24]

Some publications have described CCMs and associated pathology of other genetic origin, proved by genetic analysis.[26,27] The present case matches this series and is the first such association described in the literature.

It is worth mentioning that in most publications, associated pathology occurs in cases with familial or multiple CCMs, which supports the existence of some common mechanisms of its development. In respect to the clinical course, there are various options in the manifestation of these diseases: both of them, or only CCMs or the other disease, may be symptomatic.

In the discussed case, correct diagnosis and management led to a long-lasting

Table 1. Incidence of Comorbidities

Central Nervous System Pathology	Number of Cases	Extracerebral Pathology	Number of Cases
Migraine	12	Cutaneous angioma(s)	10
Extra-axial tumors (meningioma[s])	16 (7)	Multiple congenital anomaly syndromes	5
Intra-axial tumors	8	Congenital eye anomalies	4
Venous angioma (unrelated to CCMs) or congenital malformation of the dural sinus	7	Congenital heart defects	4
Arterial aneurysm(s)	6	Retinal disinsertion	4
Chiari malformation type I	5	Congenital kidney anomalies	3
Arachnoid cyst	5	Congenital dorsopathy	3
Neurofibromatosis type I	3	Congenital cataract	3
Multiple sclerosis	2	Cleft palate	2
Congenital hydrocephalus	2	Diabetes type 1	2
Arteriovenous malformation	2	Wilson disease	1
Pituitary dwarfism	1	Perinephric cavernous malformation	1
Schizophrenia	1	Aneurysmal cyst of zygomatic arch	1
Trigeminal neuralgia	1	Congenital lymphangioma of the face	1
Myasthenia gravis	1	Multiple subcutaneous lymphomatosis	1
Agenesis of the corpus callosum	1	Marfan syndrome	1
		Other (myocardiodystrophy, neurodermatitis, psoriasis, congenital keratomas, thrombocytopenia, erythremia)	8
Total	73 (57.5%)	Total	54 (42.5%)
Total	127 (118 patients)		

CCM, cerebral cavernous malformations.

good clinical result. It definitely demonstrates the need for further genetically based research of various pathologies and the necessity of an interdisciplinary approach in the treatment of such patients.

REFERENCES

1. McCormick WF. Pathology of vascular malformations of the brain. In: Wilson CB, Stein BM, eds. *Intracranial Arteriovenous Malformations*. Baltimore, MD: Williams and Wilkins; 1984:44-63.
2. Belousova OB, Konovalov AN. Cavernous Malformations of the Central Nervous System. Moscow: Kinovek; 2014:256 (in Russian).
3. Del Curling O Jr, Kelly DL Jr, Elster AD, Craven TE. An analysis of the natural history of cavernous angiomas. *J Neurosurg*. 1991;75:702-708.
4. Johnson EW, Zabramski JM. Genetics of cerebral cavernous malformations. In: Lanzino G, Spetzler RF, eds. *Cavernous Malformations of the Brain and Spinal Cord*. New York, NY: Thieme; 2008: 26-29.
5. Pagenstecher A, Stahl S, Sure U, Felbor U. A two-hit mechanism causes cerebral cavernous malformations: complete inactivation of CCM1, CCM2 or CCM3 in affected endothelial cells. *Hum Mol Genet*. 2009;18:911-918.
6. Schwartz AC, Weaver RG Jr, Bloomfield R, Tyler ME. Cavernous hemangioma of the retina, cutaneous angiomas, and intracranial vascular lesion by computed tomography and nuclear magnetic resonance imaging. *Am J Ophthalmol*. 1984;98:483-487.
7. Fukushima T, Ohkawa M, Tomonaga M. Multiple and familial cavernous angiomas in the brain and extremities—case report. *No Shinkei Geka*. 1986; 14(suppl 3):423-428 (in Japanese).
8. Bartolomei F, Lemarquis P, Alicherif A, Lepillouer-Prost A, Sayag J, Khalil R. Systematized cavernous angiomatosis with multiple cerebral and cutaneous localizations. *Rev Neurol (Paris)*. 1992;148:568-570 (in French).
9. Leblanc R, Melanson D, Wilkinson RD. Hereditary neurocutaneous angiomatosis. Report of four cases. *J Neurosurg*. 1996;85:1135-1142.
10. Ostlere L, Hart Y, Misch KJ. Cutaneous and cerebral haemangiomas associated with eruptive angiokeratomas. *J Dermatol*. 1996;135:98-101.
11. Labauge P, Enjolras O, Bonerandi JJ, Laberge S, Dandurand M, Joujoux JM, et al. An association between autosomal dominant cerebral cavernomas and a distinctive hyperkeratotic cutaneous vascular malformation in 4 families. *Ann Neurol*. 1999;45: 250-254.
12. Toll A, Parera E, Giménez-Arnau AM, Pou A, Lloreta J, Limaye N, et al. Cutaneous venous malformations in familial cerebral cavernomatosis caused by KRIT1 gene mutations. *Dermatology*. 2009;218:307-313.
13. Sirvente J, Enjolras O, Wassef M, Tournier-Lasserve E, Labauge P. Frequency and phenotypes of cutaneous vascular malformations in a consecutive series of 417 patients with familial cerebral cavernous malformations. *J Eur Acad Dermatol Venereol*. 2009;23:1066-1072.
14. Lan MY, Liu YF, Huang CC, Peng CH, Liu JS, Chang YY. Cavernous malformations of the central nervous system combined with cutaneous vascular lesions due to KRIT1 mutation: a case report. *Clin Neurol Neurosurg*. 2010;112:729-732.
15. Feldmeyer L, Baumann-Vogel H, Tournier-Lasserve E, Riant F, Jung HH, French LE, et al. Hyperkeratotic cutaneous vascular malformation associated with familial cerebral cavernous malformations (FCCM) with KRIT1/CCM1 mutation. *Eur J Dermatol*. 2014;24:255-257.
16. Cigoli MS, De Benedetti S, Marocchi A, Bacigaluppi S, Primignani P, Gesu G, et al. A novel MGC4607/CCM2 gene mutation associated with cerebral spinal and cutaneous cavernous angiomas. *J Mol Neurosci*. 2015;56:602-607.
17. Bilo L, Antenora A, Peluso S, Procaccini EM, Quarantelli M, Mansueto G, et al. CCM3/PDCD10 gene mutation in cerebral cavernous malformations associated with hyperkeratotic cutaneous capillary venous malformations. *J Dermatol*. 2016; 43:962-963.
18. Rerat K, Parker F, Nasser G, Vidaud D, Riant F, Tournier-Lasserve E, et al. Occurrence of multiple cerebral cavernous malformations in a patient with neurofibromatosis type 1. *J Neurol Sci*. 2015; 350:98-100.
19. Hayashi Y, Tohma Y, Mouri M, Yamashima T, Yamashita J. Congenital multiple cavernous angiomas associated with thrombosed arteriovenous malformation of the brain—case report. *Neurol Med Chir (Tokyo)*. 2002;42:67-72.
20. Arpino L, Nuzzo Di, Franco A. Pontine cavernoma and intraventricular meningioma: an unusual association. *J Neurosurg Sci*. 2011;55:397-398.
21. Gass JD. Cavernous hemangioma of the retina: a neuro-oculo-cutaneous syndrome. *Am J Ophthalmol*. 1971;71:799-814.
22. Dobyns WB, Michels VV, Groover RV, Mokri B, Trautmann JC, Forbes GS, et al. Familial

cavernous malformations of the central nervous system and retina. *Ann Neurol*. 1987;21:578-583.

23. Choudhri O, Feroze AH, Lad EM, Kim JW, Plowey ED, Karamchandani JR, et al. Co-occurrence of a cerebral cavernous malformation and an orbital cavernous hemangioma in a patient with seizures and visual symptoms: rare crossroads for vascular malformations. *Surg Neurol Int*. 2014;5(suppl 4): S148-S154.

24. Ardeshiri A, Ardeshiri A, Beiras-Fernandez A, Steinlein OK, Winkler PA. Multiple cerebral cavernous malformations associated with extracranial mesenchymal anomalies. *Neurosurg Rev*. 2008;31:11-17 [discussion: 17-18].

25. Sharma S, Tsyvine D, Maldjian PD, Sambol JT, Lovoulos CJ, Levy G, et al. An intriguing coexistence: atrial myxoma and cerebral cavernous malformations: case report and review of literature. *J Am Soc Echocardiogr*. 2011;24:110.e1-110.e4.

26. Whitworth J, Stausbøl-Grøn B, Skytte AB. Genetically diagnosed Birt-Hogg-Dubé syndrome and familial cerebral cavernous malformations in the same individual: a case report. *Fam Cancer*. 2017; 16:139-142.

27. Boutarbouch M, Ben Salem D, Giré L, Giroud M, Béjot Y, Ricolfi F. Multiple cerebral and spinal cord cavernomas in Klippel-Trenaunay-Weber syndrome. *J Clin Neurosci*. 2010;17:1073-1075.

28. Drigo P, Mammi I, Battistella PA, Ricchieri G, Carollo C. Familial cerebral, hepatic, and retinal cavernous angiomas: a new syndrome. *Childs Nerv Syst*. 1994;10:205-209.

29. Toldo I, Drigo P, Mammi I, Marini V, Carollo C. Vertebral and spinal cavernous angiomas associated with familial cerebral cavernous malformation. *Surg Neurol*. 2009;71:167-171.

30. Bicknell JM, Carlow TJ, Kornfeld M, Stovring J, Turner P. Familial cavernous angiomas. *Arch Neurol*. 1978;35:746-749.

31. Hayman LA, Evans RA, Ferrell RE, Fahr LM, Ostrow P, Riccardi VM. Familial cavernous angiomas: natural history and genetic study over a 5-year period. *Am J Med Genet*. 1982;11:147-160.

32. Gomes A, Dedoussis GV. Geographic distribution of ATP7B mutations in Wilson disease. *Ann Hum Biol*. 2016;43:1-8.

33. Keskin D, Ezirmik N, Celik H. Familial multiple lipomatosis. *Isr Med Assoc J*. 2002;4:1121-1123.

34. Toy BR. Familial multiple lipomatosis. *Dermatol Online J*. 2003;9:9.

35. Lee CH, Spence RA, Upadhyaya M, Morrison PJ. Familial multiple lipomatosis with clear autosomal dominant inheritance and onset in early adolescence. *BMJ Case Rep*. 2011;2011.

36. Schaefer M, Gotthardt DN, Didion C, Stremmel W, Weiss KH. Increased prevalence of subcutaneous lipomas in patients with Wilson disease. *J Clin Gastroenterol*. 2015;49:e61-e63.

37. Németh D, Árvai K, Horváth P, Kósa JP, Tobiás B, Balla B, et al. Clinical use of next-generation sequencing in the diagnosis of Wilson's disease. *Gastroenterol Res Pract*. 2016;2016:4548039.

38. Cullere X, Plovie E, Bennett PM, MacRae CA, Mayadas TN. The cerebral cavernous malformation proteins CCM2L and CCM2 prevent the activation of the MAP kinase MEKK3. *Proc Natl Acad Sci U S A*. 2015;112:14284-14289.

39. Cigoli MS, Avemaria F, De Benedetti S, Gesu GP, Accorsi LG, Parmigiani S, et al. *PDCD10* gene mutations in multiple cerebral cavernous malformations. *PLoS One*. 2014;9:e110438.

40. D'Angelo R, Alafaci C, Scimone C, Ruggeri A, Salpietro FM, Bramanti P, et al. Sporadic cerebral cavernous malformations: report of further mutations of CCM genes in 40 Italian patients. *Biomed Res Int*. 2013;2013:459253.

41. Rzhetsky A, Wajngurt D, Park N, Zheng T. Probing genetic overlap among complex human phenotypes. *Proc Natl Acad Sci U S A*. 2007;104: 11694-11699.

42. Goh KI, Cusick ME, Valle D, Childs B, Vidal M, Barabási AL. The human disease network. *Proc Natl Acad Sci U S A*. 2007;104:8685-8690.

43. Jin W, Qin P, Lou H, Jin L, Xu S. A systematic characterization of genes underlying both complex and Mendelian diseases. *Hum Mol Genet*. 2012;21:1611-1624.

44. Blair DR, Lyttle CS, Mortensen JM, Bearden CF, Jensen AB, Khiabanian H, et al. A nondegenerate code of deleterious variants in Mendelian loci contributes to complex disease risk. *Cell*. 2013;155: 70-80.

45. Clatterbuck RE, Cohen B, Gailloud P, Murphy K, Rigamonti D. Vertebral hemangiomas associated with familial cerebral cavernous malformation: segmental disease expression. Case report. *J Neurosurg*. 2002;97(suppl 2):227-230.

46. Zlotoff BJ, Bang RH, Padilla RS, Morrison L. Cutaneous angiokeratoma and venous malformations in a Hispanic-American patient with cerebral cavernous malformations. *Br J Dermatol*. 2007; 157:210-212.

47. Chen DH, Lipe HP, Qin Z, Bird TD. Cerebral cavernous malformation: novel mutation in a Chinese family and evidence for heterogeneity. *J Neurol Sci*. 2002;196:91-96.

48. Campione E, Diluvio L, Terrinoni A, Di Stefani A, Orlandi A, Chimenti S, et al. Progressive late-onset of cutaneous angiomatosis as possible sign of cerebral cavernous malformations. *Dermatol Online J*. 2013;19:2.

49. Furlanetti LL, Santos MV, Valera ET, Brassesco MS, de Oliveira RS. Metachronous occurrence of nonradiation-induced brain cavernous hemangioma and medulloblastoma in a child with neurofibromatosis type I phenotype. *J Pediatr Neurosci*. 2012;7:43-46.

Conflict of interest statement: Funding was provided by a grant of Russian Foundation for Basic Research (17-04-01957).

Received 1 March 2017; accepted 1 June 2017

Citation: World Neurosurg. (2017). http://dx.doi.org/10.1016/j.wneu.2017.06.002

*Journal homepage: **www.WORLDNEUROSURGERY.org***

*Available online: **www.sciencedirect.com***