



Ivy Sign in Mildly Symptomatic β -Thalassemia Intermedia, with Development of Moyamoya Disease

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SUMMARY – *Cerebrovascular occlusive disease with secondary proliferative angiogenesis can be idiopathic as a standalone disease state, known as moyamoya disease, or it may develop secondary to different disease entities, such as chronic hemoglobinopathies, in which case it is known as moyamoya syndrome. Although moyamoya syndrome has been well described with sickle cell anemia, its association with other hemoglobinopathies is rarely reported. We describe a 16-year-old girl with β -thalassemia intermedia who presented with recurrent headaches and focal seizures non-responsive to medical treatment. Magnetic resonance imaging showed diffuse intrasulcal bright signal intensity on fluid-attenuated inversion recovery and leptomeningeal enhancement previously termed the “ivy sign”, and her magnetic resonance angiography was consistent with bilateral moyamoya disease. The literature describing and explaining the pathogenesis of the “ivy sign” and its relationship to moyamoya disease was reviewed.*

Introduction

Thalassemia intermedia is considered among the milder hemoglobinopathies, but it may still be associated with ischemic changes¹. Several contributory etiologies result in hypercoagulability that may be found in thalassemia patients. These etiologies may result in associated ischemic changes and can include: blood cell membrane alteration, platelet activation, liver dysfunction, post-splenectomy thrombocytosis and cardiac failure^{2,3}. Central nervous system (CNS) ischemic manifestations may result in secondary moyamoya syndrome. The secondary presentation of moyamoya syndrome depends on the establishment of collateral vascular pathways that develop to compensate for decreased cerebral perfusion through the conventional arborizing intracranial arterial system. These potential collateral pathways in moyamoya cases include basal moyamoya perforator vessels from deep perforator vessels arising from the anterior two thirds of the circle of Willis, leptomeningeal collateral vessels from the posterior cerebral

artery (PCA), and transdural collateral vessels richly investing the leptomeninges from the external carotid artery circulation^{4,5}. The term “ivy sign” has previously been reported as a suggested sign to describe the diffuse leptomeningeal enhancement seen in certain pathologic states, as such diffuse leptomeningeal enhancement can insinuate itself within multiple sulci thereby resembling ivy covered stone walls where ivy plants can insinuate themselves within channels and cracks such as those typically found in such stone walls⁶.

Clinical Findings

A 16-year-old girl presented with the complaint of headaches increasing in both intensity and frequency over a two-year interval. She also experienced recurrent episodes of focal seizures, and was therefore referred for magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain. The family history was remarkable for both parents being first-degree cousins, and for her brother possess-

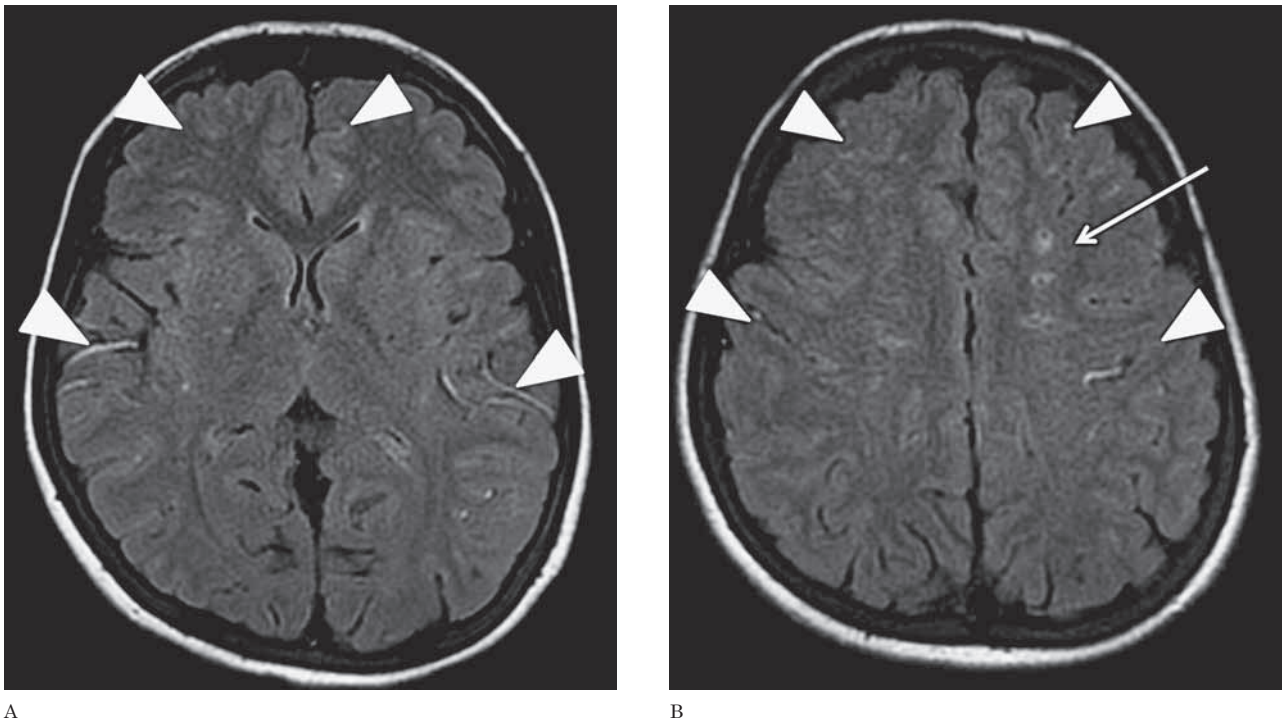


Figure 1 A,B) Axial FLAIR MR images at ventricular and supraventricular levels respectively, showing high signal intensity superficially involving the cerebral sulci and on the brain surface. The “ivy sign” (arrowheads) of conspicuous leptomeningeal hyperintensity is demonstrated with multiple foci of high signal seen in the subcortical and periventricular regions, anterior internal border zone white matter more than on the left side, signifying chronic white matter ischemic changes (arrows).

ing the β -thalassemia trait. The patient was diagnosed with thalassemia intermedia following an initial presentation at 18 months of age when she was noted to have pallor, and was diagnosed with a febrile illness due to a sore throat. As part of her work up a CBC at that time showed moderate anemia with hypochromia and microcytosis, further workup resulted in the blood film showing severe poikilocytosis and anisocytosis. Hemoglobin (Hb) electrophoresis revealed Hb A 54%, Hb A2 2.9%, Hb F 32.3%, and her DNA showed a classical mutation appearance for β -thalassemia intermedia. As part of her chronic therapeutic regimen, folic acid was started and she was followed with serial hemoglobin measurement. The patient maintained a hemoglobin level between 8.7 and 9.5 g/dl without blood transfusion, and demonstrated normal growth otherwise when measured against her peer group, with normal skeletal development. At the age of 14 she presented with multiple episodes of focal seizures manifesting as initial numbness of the right hand followed by an inability to move her limbs, concordant with peri-oral numbness with slurred speech. These episodes of focal seizures spontaneously resolved without

treatment. Most recently, on her last outpatient visit at age 16, prior to the current workup for her worsening headaches, the patient was noted to be mildly jaundiced, and continued to demonstrate a normal neurologic examination with the exception of an unchanged right-sided congenital chronic eyelid ptosis. A routine screening ultrasound examination of the abdomen performed as part of her β -thalassemia intermedia care showed mild splenomegaly, and her bone mineral density (BMD) scan showed normal bone density. An MRI was performed at an outside institution one month prior to her admission, as part of her outside headache workup; the interpretation of the outside MRI raised the possibility of meningoencephalitis. As part of her outside workup cerebrospinal fluid (CSF) samples were obtained, and inflammatory markers and CSF analysis were unremarkable. Follow-up cranial MRI and MRA showed bilateral focal hyperintensities on fluid-attenuated inversion recovery (FLAIR) images with cortical, subcortical, sulcal, periventricular and anterior internal border zone involvement, the lattermost more on the left than on the right (Figure 1). Corresponding leptomeningeal enhance-

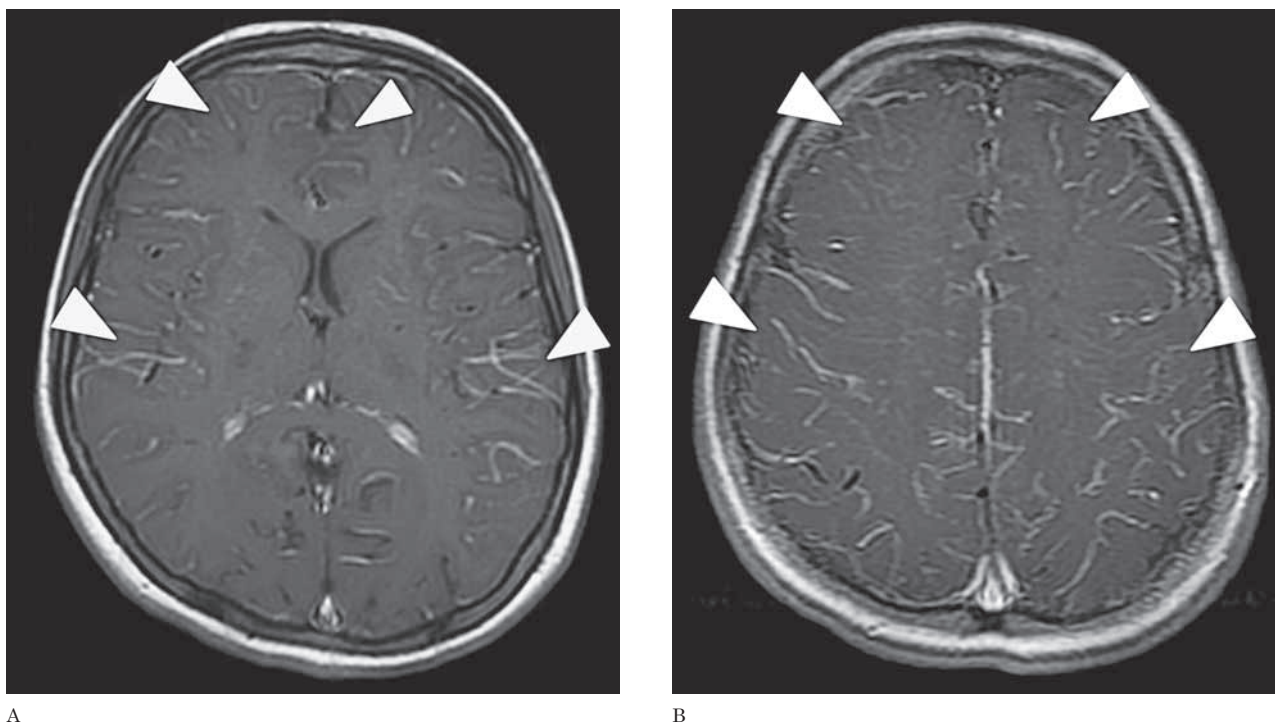


Figure 2 A,B) Axial T1-W post i.v. gadolinium image showing prominent leptomeningeal collaterals shown as linear enhancement within the cerebral sulci and overlying the brain surface involving the ACA and MCA vascular territories (arrowheads), corresponding to the FLAIR hyperintensities shown in Figure 1.

ment was demonstrated on T1 weighted (T1-W) post-contrast images involving the anterior cerebral artery (ACA) and middle cerebral artery (MCA) vascular territories diffusely (Figure 2). Cerebral MRA showed advanced large artery steno-occlusive changes of the distal intracranial internal carotid artery (ICA), in addition to involvement of the proximal ACA and MCA. There was also a demonstration of the typical reactive and proliferative cloud of collateral vessels consisting of deep perforator vessels, giving the characteristic “puff of smoke” appearance (Figure 3). These findings were consistent with a diagnosis of intracranial steno-occlusive moyamoya syndrome, in this instance demonstrating both deep and leptomeningeal collateral vessels secondary to thalassemia intermedia.

Discussion and Review

Moyamoya is a chronic and progressive cerebrovascular occlusive disease with two distinct components: a stenotic/occlusive process that slowly occludes large intracranial vessels in typically distinct locations with a sequentially

described progression, and a reactive proliferative/angiogenetic process leading to the conspicuous presence of collateral vessels as part of the body's effort to maintain distal circulation despite the steno-occlusive vasculopathy. Moyamoya was first reported by and named by Takeuchi and Shimizu in Japanese patients in 1957⁷.

There are three basic chronic collateral cerebrovascular pathways that develop in moyamoya: basal hyperproliferated moyamoya vessels from deep perforators, leptomeningeal collateral vessels arising from the posterior cerebral artery, and transdural collateral vessels arising from the external carotid artery. The stenotic/occlusive process initially involves the intracranial ICAs near the ICA termini, typically also involving the A1 and M1 segments and proceeding to more diffusely involve the basal intracranial vessels. Subsequently, the proliferative/angiogenetic process leads to the formation of collateral vessels arising from the expected vicinity of the carotid summit, attempting to supply the chronically underperfused brain tissue. These compensatory collateral moyamoya perforating lenticulostriate ves-

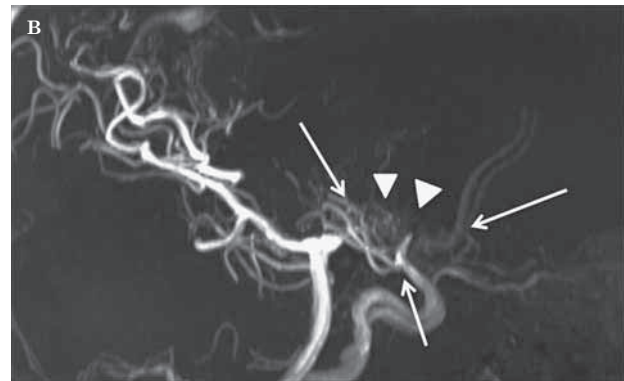
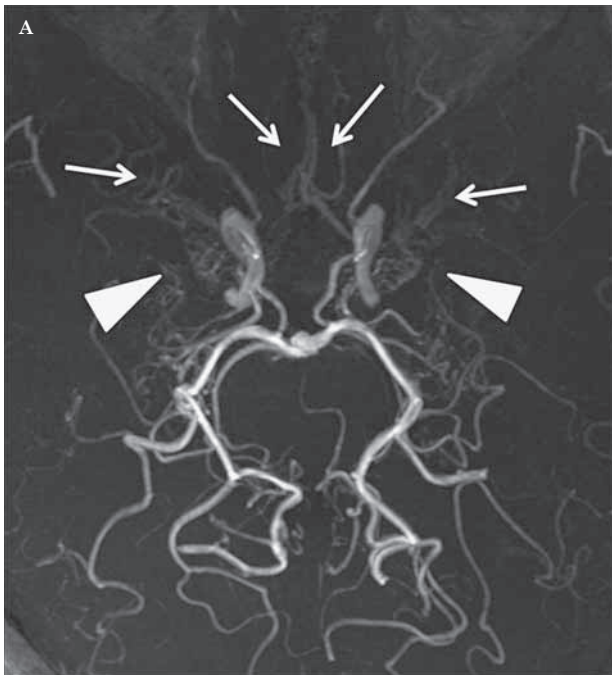


Figure 3 A,B) Maximum intensity projection (MIP) cranial MRI in axial (A) and lateral (B) orientations, showing narrowing of the bilateral supraclinoid ICAs, infracallosal ACA (A1 and A2) and proximal MCA (M1) (arrows), with development of moyamoya deep collateral vessels, including multiple associated hypertrophied lenticulostriate and thalamic perforators (arrowheads).

sels could develop with such vessel density that on catheter angiograms could generate an appearance similar to a “puff of smoke,” termed in Japanese “moyamoya.” Similarly, proliferating collateral vessels could also distinctively arise from the posterior circulation when relatively preserved as it attempts to provide collateral circulatory assistance to the affected MCA and ACA circulations, and families of fine transdural collateral vessels could separately arise from the external carotid circulation⁸. These lattermost vessels could also be distinguished within the leptomeninges as robust enhancing leptomeningeal collateral vessels, giving the ivy sign⁹. When idiopathic, the findings described are seen in moyamoya disease, and when associated with and explained by other systemic pathological processes such as hemoglobinopathies, Down syndrome, neurofibromatosis, atherosclerosis or prior cranial irradiation, etc. the above findings are considered moyamoya syndrome^{10,11}. As far as specific hemoglobinopathies are concerned, moyamoya syndrome has been specifically well described with sickle cell anemia, hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria, and Fanconi anemia. The association of moyamoya syndrome with β -thalassemia is not well recognized, and its association with β -thalassemia intermedia as in our index case is a rarity^{3,5}. β -thalassemia intermedia is frequently characterized by a mild clinical course, a hemoglobin level of more

than 7g/dl, an age of onset over two years, normal growth, a moderate requirement for blood transfusions, and iron chelation therapy is only necessitated in older β -thalassemia patients⁴. Our index case was started on folic acid at the age of five years, she maintained a baseline Hb between 8.7-9.5 g/dl without blood transfusions, and she maintained normal growth with no abnormal skeletal findings. In patients with β -thalassemia intermedia hypoxia caused by low levels of hemoglobin stimulates hypertrophic changes of the endothelium and microvascular stenosis. Other factors causing hypercoagulability in β -thalassemia patients, namely blood cell membrane alteration, platelet activation, liver dysfunction, post-splenectomy thrombocytosis and cardiac failure also compound tissue hypoxia. Moreover, the depletion of lipid antioxidant to cope with oxidative stress may result in low-density lipoproteins reduction, with higher atherogenic potentials compounding the formation of stenosis⁴. Moyamoya vessels are often considered to evolve through stages of stenosis, recruitment, and finally involution. Steno-occlusive changes of the supraclinoid ICA were classified into six typically sequential angiographic stages as defined by Suzuki et al¹²: stage I, stenosis of the distal intracranial (supraclinoid) ICA; stage II, appearance of moyamoya vessels as a result of functional stage I hypoperfusion; stage III, partial steno-proximally with occlusive changes (discontinuity) of the MCA

and ACA cerebral arteries and an associated increase in proliferating perforators including occasional prominence of PCA collateral supply; stage IV, discontinuity or disappearance of the posterior communicating artery (PcoA) with disappearance of either or none of the ICA, ACA and MCA trunks; stage V, more advanced steno-occlusive changes with further disappearance of the ACA and MCA associated with a reduction in number and prominence of the proliferative moyamoya vessels; and stage VI, collateral recruited blood supply exclusively from the external carotid arteries with almost complete disappearance of the proliferative moyamoya vessels¹¹. Where leptomeningeal PCA collateral supply is specifically concerned in a pediatric moyamoya population undergoing serial angiographic comparisons, PCA collaterals are demonstrated to be most richly developed with stages II or III, and show a progressive decrease from stage III to VI coinciding with PCA steno-occlusive changes¹³. When specifically assessing the incidence of such sequential changes in patients with β -thalassemia intermedia, a 27.6% incidence of discernible arterial stenosis in patients with thalassemia intermedia has been reported. Of these patients, 75% had a single stenosed cerebral artery and 25% had more than one artery involved. The ICA was most commonly involved, and was stenosed in 75%. The stenosis was mild in 75% of patients, severe (>75%) in 16.7%, and only moderate in 8.3%. Aneurysms were also identified in 17.2% of a β -thalassemia intermedia patient sample examined, a higher incidence than would be expected in a normal population in which an incidence of 0.2 to 9.9 percent is expected¹³.

Asymptomatic brain infarcts occur in 37.5% of patients with β -thalassemia intermedia and 52% of patients with sickle cell thalassemia disease. Typically, such infarcts occur in patients over 20 years of age, and are unusual in younger patients such as ours, although there have been reports of pediatric cases with β -thalassemia intermedia presenting with transient ischemic attacks. Silent ischemic brain lesions are typically classified according to size as small (<0.5 cm), medium (0.5-1.5 cm), or large (>1.5 cm), and are usually located in the deep white matter and/or basal ganglia. Patients with β -thalassemia intermedia more often possess small (55.5%) or medium (38.9%) lesions, with only 5.6% having large lesions^{4,11}. Brain MRI and MRA could therefore be used to identify otherwise neurologically asymptomatic patients with minor hemoglobinopathies who have already demon-

strated silent ischemic changes, and are at risk for stroke. Such assessment could potentially provide such patients the opportunity to be prophylactically treated with transfusional (for β -thalassemia intermedia) or pharmacologic (for sickle cell-thalassemia disease) therapies if their MRI and MRA examinations show the unsuspected steno-occlusive and angioproliferative findings of CNS moyamoya, or silent ischemic changes. As specifically regards diffuse leptomeningeal T1-weighted contrast enhancement in moyamoya patients, also known as the "ivy sign", this finding and nomenclature was first reported by Ohta et al. in 1995⁶. The observation was made that diffuse leptomeningeal enhancement may resemble partially ivy-covered stone walls where ivy plants can insinuate themselves within channels and cracks such as those typically found in such stone walls¹⁴. Subsequently, similar leptomeningeal high signal intensity has been reported on unenhanced FLAIR images and is therefore also similarly referred to as demonstrating the ivy sign^{7,13,14}.

Two hypotheses have been proposed to explain the ivy sign seen in children with moyamoya syndrome including: direct visualization of engorged pial vasculature due to either slowed retrograde flow in transpial vessels or dilated pial vessels, or congested thickening of the leptomeninges^{9,14}. At least one scoring system regarding the ivy sign has been developed for FLAIR images utilizing both anatomic discrimination and regional conspicuity of the ivy sign¹³. The cortical-subcortical region of each cerebral hemisphere is divided into the following four anatomic vascular regions: the ACA, the anterior half of the MCA region (ant-MCA), the posterior half of the MCA region (post-MCA), and the region of the PCA. The ant-MCA and post-MCA regions are separated by the central sulcus, and the temporal lobe is assigned to the post-MCA region. A numerical grade of 0, 1 or 2 is then assigned to the predominance of leptomeningeal conspicuity (ivy sign score). In this scheme, zero is an absence of the ivy sign, grade 1 means that the ivy sign is seen on less than half of the cortical surface for that anatomic region, and grade 2 indicates that the ivy sign involves more than half of the cortical surface for that particular anatomic region. Utilizing this semiquantitative approach the ivy sign was most frequently and prominently seen in the anterior part of the MCA region. The conspicuity of the ivy sign (summed in each hemisphere) showed a significant correlation with the severity of ischemic symptoms, an inverse correla-

tion with the resting cerebral blood flow, and a stronger inverse correlation with the cerebral vascular reserve CVR: the latter may prove to be a more reliable predictor of subsequent ischemic stroke¹⁴. When examining the risk factors demonstrating discernible steno-occlusive changes of the supraclinoid ICA on MRA, both the mean total hemoglobin level is significantly lower in patients with evidence of stenosis than those without (71.3 vs. 91.1 g/L), and also the mean non-transferrin-bound iron level is significantly higher in patients with evidence of stenosis than those without (6.4 vs. 2.3 μ mol/L). When examining other suspected associated findings in such patients, no significant correlation can be drawn between evidence of stenosis on MRA and age, gender, transfusion history, nucleated red blood cell count, platelet count, serum ferritin level, or liver iron concentration⁶. Definitive treatment of moyamoya disease includes direct or indirect vascular bypass surgery. Where surgical treatment is concerned, a postoperative decrease in ivy sign correlates with improved hemodynamic status of the surgically treated hemisphere¹⁵.

References

- 1 Golden G. Stroke syndromes in children. *Neurol Clin.* 1985; 3 (1): 59-75.
- 2 Merkel KH, Ginsberg PL, Parker JC Jr, et al. Cerebrovascular disease in sickle cell anemia: a clinical, pathological and radiological correlation. *Stroke.* 1978; 9 (1): 45-52. doi: 10.1161/01.STR.9.1.45.
- 3 Oberoi S, Bansal D, Singh P, et al. Stroke in a young boy with β -thalassemia intermedia secondary to Moyamoya syndrome. *J Pediatr Hematol Oncol.* 2010; 32 (7): 568-570. doi: 10.1097/MPH.0b013e3181ed0e84.
- 4 Manfrè L, Giarratano E, Maggio A, et al. MR imaging of the brain: findings in asymptomatic patients with thalassemia intermedia and sickle cell-thalassemia disease. *Am J Roentgenol.* 1999; 173 (6): 1477-1480.
- 5 Karimi M, Khanlari M, Rachmilewitz E. Cerebrovascular accidents in thalassemia major and thalassemia intermedia. *Am J Hematol.* 2008; 83: 77-79. doi: 10.1002/ajh.20938.
- 6 Ohta T, Tanaka H, Kuroiwa T. Diffuse leptomeningeal enhancement, "ivy sign," in magnetic resonance images of moyamoya disease in childhood: case report. *Neurosurgery.* 1995; 37 (5): 1009-1012. doi: 10.1227/00006123-199511000-00024.
- 7 Oshima H, Katayama Y. Discovery of cerebrovascular moyamoya disease: research during the late 1950s and early 1960s. *Childs Nerv Syst.* 2012; 28 (4): 497-500. doi: 10.1007/s00381-012-1708-x.
- 8 Yoon H, Shin H, Chang Y. "Ivy sign" in childhood moyamoya disease: depiction on FLAIR and contrast-enhanced T1-weighted MR images. *Radiology.* 2002; 223 (2): 384-389. doi: 10.1148/radiol.2232011094.
- 9 Farrugia M, Howlett D, Saks A. Moyamoya disease. *Postgrad Med J.* 1997; 73 (863): 549-552. doi: 10.1136/pgmj.73.863.549
- 10 El Beltagi A, El-Nil H, Norbash A, et al. Unilateral basal ganglia infarcts: a red flag for ipsilateral cervical arterial occlusive disease. A report on two children with Moyamoya disease. *Neuroradiol J.* 2012; 25 (1): 89-97.
- 11 Musallam K, Beydoun A, Hourani R, et al. Brain magnetic resonance angiography in splenectomized adults with β -thalassemia intermedia. *Eur J Haematol.* 2011; 87 (6): 539-546. doi: 10.1111/j.1600-0609.2011.01706.x.
- 12 Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. *Arch Neurol.* 1969; 20 (3): 288-299. doi: 10.1001/archneur.1969.00480090076012.
- 13 Mugikura S, Takahashi S, Higano S, et al. The relationship between cerebral infarction and angiographic characteristics in childhood moyamoya disease. *Am J Neuroradiol.* 1999; 20 (2): 336-343.
- 14 Mori N, Mugikura S, Higano S, et al. The leptomeningeal "ivy sign" on fluid-attenuated inversion recovery MR imaging in Moyamoya disease: a sign of decreased cerebral vascular reserve? *Am J Neuroradiol.* 2009; 30 (5): 930-935. doi: 10.3174/ajnr.A1504.
- 15 Kawashima M, Noguchi T, Takase Y, et al. Decrease in leptomeningeal ivy sign on fluid-attenuated inversion recovery images after cerebral revascularization in patients with Moyamoya disease. *Am J Neuroradiol.* 2010; 31 (9): 1713-1718. doi: 10.3174/ajnr.A2124.

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