

## Moyamoya disease

Felipe Farias Serratos<sup>3</sup>, Tatsuya Ishikawa<sup>1</sup>, Yasuji Yoshida<sup>1</sup>, Junta Moroi<sup>1</sup>, Motoshi Sawada<sup>1</sup>, Norikata Kobayashi<sup>1</sup>, Tatsushi Mutoh<sup>1</sup>, Ren Jun<sup>2</sup>,  
Claudia V. Farias Serratos<sup>3</sup>

### ABSTRACT

Moyamoya disease (MMD) was reported by first time in 1957 by Takeuchi and Shimizu as hypoplasia of the bilateral internal carotid arteries. The official Japanese name for the disease is Spontaneous occlusion of the circle of Willis, but in 1967 Suzuki and Takaku nicknamed it Moyamoya disease. In Japan, the estimated total number of the patients with this disease was 3900 in 1995 and the annual incidence is 0.35 per 100,000 populations. The incidence of the disease is high among Japanese and Koreans and far lower in Caucasians. On the other hand, in Western countries there is not reliable epidemiological data about it. The male and female ratio was 1:1.7 showing a slight female predominance. Solitary cases are much more frequent but familial cases were reported approximately in 10% with 13 cases of monovular twins. Moyamoya disease may cause cerebral ischemia (transient ischemic attacks and infarction) and haemorrhage (intracerebral, intraventricular and subarachnoid). Symptoms and signs in children are mainly TIA (hemiparesis, monoparesis and sensory disturbance), which occur repeatedly and occasionally. Headache, involuntary movements is and convulsive seizures may occur. Despite extensive studies over a long period, the aetiology of Moyamoya disease is still no clear. Because of the higher incidence of this disease in Orientals, very low incidence in Caucasians, and the presence of familial cases, multifactorial inheritance is considered to be causative. The treatments for Moyamoya disease are both medical and surgical. There are no medical treatments to prevent the progression of the illness. Direct bypass surgery (superficial temporal artery to middle cerebral artery,

STA-MCA anastomosis) or indirect bypass surgery (placing the vascularized soft tissue flap on the surface of brain) can improve the decreased cerebral circulation and clinical signs. Indirect bypass surgery is preferred for young children. Within a few months after bypass surgery ischemic attacks disappear in most patients.

**Key words:** moyamoya, hypoplasia, treatment, carotid arteries.

### ENFERMEDAD DE MOYAMOYA

#### RESUMEN

La enfermedad de Moyamoya es una hipoplásia bilateral de las arterias carótidas muy frecuente en Japón y rara en caucásicos con predominancia en mujeres, puede producir isquemia cerebral con ataques isquémicos y/o hemorragia y producir movimientos involuntarios o convulsiones. Su etiología no es conocida. El tratamiento es la cirugía con comunicación de la arteria temporal a la cerebral media o aplicación de un injerto muscular en la corteza cerebral con lo que los ataques isquémicos desaparecen.

**Palabra clave:** Moyamoya, hipoplasia, tratamiento, arterias carótidas.

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<sup>1</sup>Neurosurgical Department of the Research Institute for Brain and Blood Vessels- Akita, Japan. <sup>2</sup>Neurosurgical Department of the Second Hospital, Lan Zhou University, China. <sup>3</sup>Neurosurgical Department, Regional Hospital of High Specialty, León, Guanajuato, México (HRAEB).

## HISTORY

**M**oyamoya disease (MMD) was reported by first time in 1957 by Takeuchi and Shimizu as hypoplasia of the bilateral internal carotid arteries. Various reports followed and the dense vascular network of the disease was gradually considered as being secondary or collateral after stenosis or occlusion of arteries. Thus, the disease has been considered acquired in origin and non congenital. The official Japanese name for the disease is spontaneous occlusion of the circle of Willis, but in 1967 Suzuki and Takaku<sup>3</sup> nicknamed it moyamoya disease, which gained worldwide usage. The Japanese term Moyamoya means a smokey, hazy or vague state like cigarette smoke, which was used to define the abnormal vascular network on angiograms. Suzuki and Takaku also sub classified the chronological stages of the disease: **1.** Narrowing of the carotid siphon, **2.** Initiation, **3.** Intensification, **4.** Minimization, **5.** Reduction, and **6.** Disappearance of Moyamoya vessels. Since 1977, a national research committee for the disease has been organized in Japan.

## EPIDEMIOLOGY

In Japan, the estimated total number of the patients with this disease was 3900 in 1995 and the annual incidence is 0.35 per 100,000 populations. The incidence of the disease is high among Japanese and Koreans and far lower in Caucasians. On the other hand, in western countries there is not reliable epidemiological data about it.

The male and female ratio was 1:1.7 showing a slight female predominance. Solitary cases are much more frequent but familial cases were reported approximately in 10% with 13 cases of monovular twins. The risk of occurrence in the patient's parents and siblings was 30-40 folds higher than that of the general population.

In Japan, the disease is distributed among all age groups, but predominates in the age group of less than 10 years. There is a low peak from 30s to 40s.

As we can see this particular distribution by age and its familiar distribution, since some time ago there are several suspicions of the presence of influenced genetics components like, for example: human leukocyte antigen (HLA) B51 and the combination HLA B51- HLA DR4 that are more frequent in patients with moyamoya disease than in asymptomatic people. In this kind of patients it has been describe the presence of a possible defect in the chromosome 3p24.2-26. There are articles that associate the disease with

autoimmune pathologies (basically the thyroid expression), and it has been related with disorder of the collagen, Down syndrome and other pathologies but these cases should not be considerate like moyamoya disease, they belonged a special group called moyamoya syndrome.

## PHYSIOPATHOLOGY

For a better understanding of vascular changes of the disease is necessary to distinguish between primary and secondary lesion. First happen the progressive decreasing of the vascular diameter and then different changes in the cerebral vascular architecture.

### Primary lesion

This is an increasing of internal tunic, unknown aetiology, it begins in distal portion of carotid artery, and at least in early phase of the disease it spreads until the anterior portion of Willis polygon, in 10% of cases lesions begin unilaterally, but in more than 75% of cases, after three years, both side are affected.

Histopathological changes consist in a fibromuscular transformation of intima tunic, a simultaneous proliferation of elastic fibbers that takes to a progressive eccentric increasing of the affected vessel and finally to the decreasing of the diameter. The internal elastic plate has torsions and folds and a degeneration of medial plate without inflammatory changes.

These transformations have been seen in extracranial vessels, and posterior cerebral circulation.

### Secondary lesion:

It is known like this, to all collateral vessels *de novo* that appear to offset critical decreasing of regional cerebral blood flow (rCBF) due to progression of primary lesion. Here is possible to distinguish an intracerebral collateral system and another extracranial. In early phases of disease, is the intracerebral collateral system who try to offset ischemic in the affected vascular territories, in the typical way of "moyamoya vessels" (*rete mirabilis*).

New vessels originate overcoat in the anterior segment of Willis polygon and form complex channels that normally connect distal portions of anterior cerebral artery (ACA) territory with medial cerebral artery (MCA). These moyamoya vessels show also pathological changes, like, irregular internal elastic plate, duplication and stenosis that even can develop

aneurysm, which, by its structural weakness could bleed and are responsible of intracerebral haemorrhagic events in adult age.

### CLINICAL FEATURES

Moyamoya disease may cause cerebral ischemia (transient ischemic attacks and infarction) and haemorrhage (intracerebral, intraventricular and subarachnoid)<sup>12</sup>. Symptoms and signs in children are mainly TIA (hemiparesis, monoparesis and sensory disturbance), which occur repeatedly and occasionally. Headache, involuntary movement and convulsive seizures may occur. The attacks are liable to occur after crying, blowing on hot noodles or playing the harmonica, all of which may cause hyperventilation resulting in constriction of cerebral arteries. After the progression of the illness, cerebral infarction may occur and fixed neurological deficits and mental retardation may follow. Intracerebral haemorrhage, severely disabled and lethal outcomes may follow.

As a result of the chronic obliteration, small collateral vessels arise distal to the blocked vessels. The idiopathic or primary form of moyamoya disease, which is sometimes familial, has to be distinguished from the secondary form, referred to as moyamoya syndrome, which can be associated with certain systemic conditions such as sickle cell disease, chronic basilar meningitis, neurofibromatosis, X-ray irradiation, homocystinuria and Down syndrome. The association of Down syndrome and moyamoya syndrome has been infrequently reported in the paediatric literature; less than 16 cases have been described in English language publications.

### DIAGNOSIS

The clinical diagnosis should depend on cerebral angiography. The diagnostic criteria are: **a.** Stenosis or occlusion of the terminal portions of the internal carotid arteries and proximal portions of the anterior and/or middle cerebral arteries, **b.** abnormal vascular networks seen in the arterial phase in the vicinity of the arterial occlusion, and **c.** bilateral involvement. Recently (MRI) magnetic resonance imaging and DR angiography (MRA) have made the diagnosis possible without using conventional angiography. Bilateral involvement is called a definite case; unilateral involvement is a probable case. The probable cases in childhood are likely to progress to bilateral lesions within 1 or 2 years, whereas those in adulthood tend to remain unchanged.

EEG is sometimes a useful examination in moyamoya disease in childhood. The characteristic finding is a rebuild up of slow waves 20-60 seconds after cessation of hyperventilation. The rebuild up phenomenon is considered to be related to decreased perfusion reserve of the ischemic brain. When cerebral ischemia is relieved by bypass surgery, the decreased perfusion reserve improves and the rebuild up phenomenon disappears. However, hyperventilation should be carefully limited because it may induce an ischemic attack. Positron emission tomography (PET) and single photon emission CT (SPECT) give important information on the cerebral perfusion and metabolism. The finding of decreased perfusion reserve is a good indication for bypass surgery.

Shinya Sato, *et al* reported the use of a single photon emission computed tomography and a novel tracer, 123I-iomazenil, to measure Central benzodiazepine (BZD) receptor density in the brain. Evaluation of early and late images was performed in asymptomatic, unoperated patients, and mildly symptomatic, operated patients.

The neuron density was preserved in adult asymptomatic patients despite harboring moyamoya disease. In contrast, the neuronal density was decreased in symptomatic patients even though their symptoms were mild and they had undergone revascularization.

### NEUROPATHOLOGICAL FINDINGS

It is rare, especially in childhood, to obtain an autopsy specimen of moyamoya disease because the mortality is very low. At surgery, it is impossible to obtain a specimen of the involved artery. Therefore the materials available for the histopathologic examination are usually those obtained by autopsy of adult patients who have died from intracranial hemorrhage.

The main lesions of the arteries are located in the anterior half of the Willis polygon. The lumina of the arteries are narrowed or occluded by a thickening of the intima. The distal portion of the basilar artery is narrowed in some patients.

Histopathologically, the intima of the mayor arteries shows eccentrically laminated thickening and the terminal elastic lamina is markedly tortuous and is duplicated in some parts. The thickened intima contains increased number of smooth muscle cells which are considered to be synthetic type smooth muscle cells migrating from the media. The media is generally attenuated. Disruption of the internal elastic lamina and inflammatory cell infiltration are generally

absent. Deposits of lipid are rare. Mural thrombi are frequently seen in the stenotic lesions, and the organization of repeated mural thrombi is suspected by some authors to be responsible for multilayered eccentric intimal thickening.

The perforating arteries in the basal ganglia, thalamus and internal capsule are either dilated with relatively thin walls or stenotic with thick walls.

### ETIOLOGY

Despite extensive studies over a long period, the etiology of moyamoya disease is still no clear. Because of the higher incidence of this disease in Orientals, very low incidence in Caucasians, and the presence of familial cases, multifactorial inheritance is considered to be causative. Significantly elevated basic-fibroblast growth factor (b-FGF) in the cerebrospinal fluid in moyamoya patients and increased activity of b-FGF and its receptor in the superficial temporal artery suggest involvement of vascular growth factors and cytokines in the disease process. Recent genetic studies of familial moyamoya disease have suggested some responsible genetic loci in chromosome 3,6, and 17.

The moyamoya disease is a clinical entity of unknown etiology, therefore, known diseases with similar angiographic findings have to be excluded like: atherosclerosis, autoimmune disorders, meningitis, brain tumors, Down syndrome, von Recklinghausen disease, head trauma, post radiation state.

The mechanism of vascular obstruction in Down syndrome with moyamoya syndrome is not known. The presence of protein C deficiency in this child raises the possibility of a thromboembolic phenomenon secondary to the deficiency.

Andeejani *et al* had reported an association between protein C deficiency and moyamoya disease resulting in cerebral infarction. A recent report by Akgun *et al* describes the association between protein S deficiency and strokes in moyamoya syndrome.

In the past 35 years, there have been a total of 60 reported cases in the literature of moyamoya syndrome after cranial irradiation, of which 52 are children.

External beam radiation is widely accepted as an essential component of effective therapy for a variety of brain tumors, but the risks of this therapy must be considered together with potential benefits. Although radiation is known to cause a small vessel microangiopathy, large vessel disease in response to radiation therapy is much more rarely reported. In this study of

345 patients who were treated with radiation therapy and then prospectively followed for up to 15 years, they identified moyamoya syndrome as an important late effect of radiation therapy. In their cohort, the majority of patients with moyamoya had a diagnosis of optic system glioma; half of these patients also carried the diagnosis of NF1. They concluded that children with brain tumors, particularly of the suprasellar region, are at substantial risk of moyamoya after radiation therapy, particularly if they also carry a diagnosis of NF1.

### TREATMENT AND PROGNOSIS

The treatments for moyamoya disease are both medical and surgical. There are no medical treatments to prevent the progression of the illness. Direct bypass surgery (superficial temporal artery to middle cerebral artery, STA-MCA anastomosis) or indirect bypass surgery (placing the vascularized soft tissue flap on the surface of brain) can improve the decreased cerebral circulation and clinical signs. Indirect bypass surgery is preferred for young children. Within a few months after bypass surgery ischemic attacks disappear in most patients.

### MOYAMOYA DISEASE AND ANESTHESIA

Because of cerebral blood flow and metabolism are severely impaired in most cases of MMD, perioperative stroke occasionally occurs after surgery. The importance of anesthetic management has therefore been emphasized. Not only hypocapnia but also hypercapnia during the operation increases the risk of perioperative stroke because hypercapnia sometimes induces the steal phenomenon of the rCBF (regional cerebral blood flow). As a result, normocapnia with a Paco<sub>2</sub> (partial pressure of carbon dioxide) value of between 38 and 40 mm Hg has been recommended during surgery for MMD. Ken-ichiro Kikuta *et al*, says in summary, intravenous anesthesia with propofol has potential to provide brain protection and preservation of rCBF in the frontal lobes in surgery for MMD. Whether choice of anesthetic agents might be important in surgery for MMD should be investigated further.

### INTELLECTUAL DECLINE IN CHILDREN WITH MOYAMOYA

AM Hogan, *et al* reported a significant intellectual decline in non- Japanese children with MMS (Moyamoya syndrome), with and without concomitant



SCA (stroke and sickle cell anaemia). Results suggest that the pace and extent of decline in individual children may be unpredictable, indicating that intellectual status should be routinely documented in individual patients. On diagnosis of MMS, it is recommended that children should have a comprehensive baseline neuropsychological assessment and that this should be reviewed at regular intervals. More data on the efficacy of surgery are required, but if benefit is proved, cognitive function in children with MMS should be closely monitored so that surgery can be considered at the earliest opportunity.

### NEURONAL LOSS IN ADULT MOYAMOYA DISEASE

Shinya Sato, Reizo Shirane, et al used a single photon emission computed tomography and a novel tracer, 123I-iodazepam, to measure BZD (Central benzodiazepine) receptor density in the brain. Evaluation of early and late images was performed in three asymptomatic, unoperated patients, and six mildly symptomatic, operated patients with MMD. The neuron density was preserved in asymptomatic adult patients despite harboring moyamoya disease. In contrast, the neuron density was irreversibly decreased in symptomatic patients even though their symptoms were mild and they had undergone revascularization.

### BIBLIOGRAFÍA CONSULTADA

1. Takeuchi K, Shimizu K. Hypoplasia of the bilateral internal carotid arteries. *No To Shinkei* 1957; 9: 37-43.
2. Kudo T. Spontaneous occlusion of the circle of Willis: A disease apparently confined to Japanese. *Neurology* 1968; 18: 485-96.
3. Suzuki J, Takaku A. Cerebrovascular 'Moyamoya disease': A disease showing abnormal net-like vessels in base of brain. *Arch Neurol* 1969; 20: 288-99.
4. Fukui M, Kawano T. Follow up study of registered cases in 1995. In: Fukui M (ed.). Annual report 1995 of the research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya disease). Tokyo: Ministry of Health and Welfare, Japan, 1996: 12-6.
5. Aoyagi M, Ogami K, Matsushima Y, Shikata M, Yamamoto M, Yamamoto K. Human leukocyte antigen in patients with moyamoya disease. *Stroke* 1995; 26: 415-7.
6. Ikeda H, Sasaki T, Yoshimoto T, Fukui M, Arinami T. Mapping of a familial moyamoya disease gene to chromosome 3p24.2-p26. *Am J Hum Genet* 1999; 64: 533-7.
7. Vila-Herrero E, Padilla-Parrado F, Vega-Pérez J, García-Casares N, Heras-Pérez J, Romero-Acebal M. Síndrome de moyamoya y displasia arterial asociados a síndrome de Down. *Rev Neurol* 2004; 34: 943-5.
8. Leno C, Mateo I, Cid C, Berciano J, Sedano C. Autoimmunity in Down's syndrome: another possible mechanism of moyamoya disease. *Stroke* 1998; 29: 868-9.
9. Fukui M. Guidelines for the diagnosis and treatment of spontaneous occlusion of the circle of Willis ('moyamoya' disease). Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) of the Ministry of Health and Welfare, Japan. *Clin Neurol Neurosurg* 1997; 99 (Suppl 2): S238-40.
10. Horn P, Pfister S, Bueltmann E, Vajkoczy P, Schmiedek P. Moyamoya like vasculopathy (moyamoya syndrome) in children. *Childs Nerv Syst* 2004; 20: 382-91.
11. Handa H, Yonekawa Y, Goto Y. Analysis of the filing data bank of 1500 cases of spontaneous occlusion of the circle of Willis and follow-up study of 200 cases for more than 5 years. In: Handa H (ed.). Annual Report (1984) of Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya disease). Tokyo: Ministry of Health and Welfare, Japan, 1985: 14-22.
12. Oka K, Yamashita M, Sadoshima S, Tanaka K. Cerebral hemorrhage in Moyamoya disease at autopsy. *Virchow Arch (A)* 1981; 392: 247-61.
13. Cramer SC, Robertson RL, Dooling EC, Scout RM. Moyamoya and Down syndrome. Clinical and radiological features. *Stroke* 1996; 27:2131-5.
14. Kitahara T, Ariga N, Yamaura A, Makino H, Maki Y. Familial occurrence of moyamoya disease: report of three Japanese families. *J Neurol Neurosurg Psychiatry* 1979; 42:208-14.
15. Aylett SE, Britton JA, De Sousa CMCP. Down syndrome and moyamoya disease: presentation with subarachnoid hemorrhage. *Pediatr Neurol* 1996; 14:259-61.
16. Takeda K, Takahashi S, Higano S, Kurihara N, Haginoya K, Shirane R, et al. Cortical laminar necrosis in a patient with moyamoya disease associated with Down syndrome. *Radiat Med* 1997; 15: 59-63.
17. Takanashi J, Sugita K, Honda A, Niimi H. Moyamoya syndrome in a patient with Down syndrome presenting with chorea. *Pediatr Neurol* 1993; 9:396-8.
18. Ogawa A, Nakamura N, Yoshimoto T. Cerebral blood flow in Moyamoya disease. Part 2: autoregulation and CO2 response. *Acta Neurochir (Wien)* 1990; 105: 30-4.
19. Fukui M. Guideline for the diagnosis of spontaneous occlusion of the circle of Willis. In: Fukui M (ed.). Annual Report (1994) of Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya disease). Tokyo: Ministry of Health and Welfare, Japan, 1995.
20. Kodama N, Aoki Y, Hiraga H, Wada T, Suzuki J. Electroencephalographic findings in children with moyamoya disease. *Arch Neurol* 1979;36:16-9.
21. Abe H, Kazumata K, Kuroda S, Houkin K. Regional cerebral hemodynamics during rebuild up phenomenon in childhood moyamoya disease-analysis by using gg-Tc-HMPAO SPECT. Annual report of 1993 of the Research Committee on Spontaneous occlusion of the circle of Willis (moyamoya disease) of the Ministry of Health and Welfare, Japan, 88-94.
22. Ikezaki K, Matsushima T, Kuwabara Y, Suzuki SO, Nomura T, Fukui M. Cerebral circulation and oxygen metabolism in childhood moyamoya disease: a perioperative positron emission tomography study. *J Neurol* 1994;81:843-50.
23. Taki W, Yonekawa Y, Kobayashi A. Cerebral circulation and oxygen metabolism in moyamoya disease of ischemic type in children. *Child Nerv Syst* 1988; 4:259-62.
24. Evaluation of Neuronal Loss in Adult Moyamoya Disease by 123I-iodazepam SPECT. Shinya Sato, Reizo Shirane, Shin Maruoka, and Takashi Yoshimoto. *Surg Neurol* 1999;51:158-63.
25. Hanakita J, Kondo A, Ishikawa J. An autopsy case of moyamoya disease. *No Shinkei Geka* 1982; 10: 531-9.
26. Hosoda Y. A pathomorphological analysis of so-called

- 'spontaneous occlusion of the circle of Willis' (Cerebrovascular moyamoya disease). *No To Shinkei* 1974; 26: 471-81.
27. Hosoda Y. Pathology of so-called 'spontaneous occlusion of the circle of Willis'. *Pathol Annu* 1984; 19: 221-4.
  28. Handa H, Tani K, Kajiura H. Autopsy case of so-called arterial rete in an adult. *No To Shinkei* 1969; 21: 181-91.
  29. Yamashita M, Oka K, Tanaka K. Histopathology of the brain vascular networks in moyamoya disease. *Stroke* 1983;14:50-8.
  30. Yamashita M, Oka K, Tanaka K. Cervico-cephalic arterial thrombi and thromboemboli in moyamoya disease, possible correlation with progressive intimal thickening in the intracranial major arteries. *Stroke* 1984; 15: 264-70.
  31. Ikeda E, Hosoda Y. Distribution of thrombotic lesions in the cerebral arteries in spontaneous occlusion of the circle of Willis: Cerebrovascular moyamoya disease. *Clin Neuropathol* 1993; 12: 44-8.
  32. Hosoda Y, Ikeda E, Hirose S. Histopathological studies on spontaneous occlusion in the circle of Willis (Cerebrovascular moyamoya disease). *Clin Neurol Neurosurg* 1997;(S.2):203-8.
  33. Masashi Fukui, Shinji Kono, Katsuo Sueishi and Kiyonobu Ikezaki. Moyamoya disease. *Neuropathology* 2000; 20, 61-4.
  34. Fukui M. Current state of study on moyamoya disease in Japan. *Surg Neurol* 1997; 47: 138-43.
  35. Takahashi A, Yukata S, Koyohiro H. The cerebrospinal fluid in patients with moyamoya disease contains high level of basic fibroblast growth factor. *Neuroscience Letter* 1993;160:214-6.
  36. Suzuki H, Hoshimaru M, Takahashi JA. Immunohistochemical reactions for fibroblast growth factor in arteries of patients with moyamoya disease. *Neurosurgery* 1994; 35: 20-5.
  37. Ikeda H, Sasaki T, Yoshimoto T. Mapping of familial moyamoya disease gene to chromosome 3p24.2-p26. *Am J Hum Genet* 1999; 64: 533-7.
  38. Inoue TK, Ikezaki K, Sasazuki T. DNA typing of HLA in patients with moyamoya disease. *Jpn H Human Genet* 1997;42: 507-15.
  39. Inoue TK, Ikezaki K, Sasazuki K. Linkage analysis of moyamoya disease on chromosome 6. *J Child Neurol* 2000; 15: 179-82.
  40. Yamauchi T, Tada M, Houkin K. Linkage of familial moyamoya disease (spontaneous occlusion of the circle of Willis) to chromosome 17q25. *Stroke* 2000; 31: 930-5.
  41. Andeejani AM, Salih MA, Kolawole T, Gader AM, Malabarey TO, al Damegh S. Moyamoya disease with unusual angiographic findings and protein C deficiency: review of the literature. *J Neurol Sci* 1998; 159: 11-6.
  42. Akgun D, Yilmaz S, Senbil N, Aslan B, Gurer YY. Moyamoya syndrome with protein S deficiency. *Eur J Pediatr Neurol* 2000; 4: 185-8.
  43. Nishizawa S, Ryu H, Yokoyama T. Post-irradiation vasculopathy of intracranial major arteries in children-report of two cases. *Neurol Med Chir (Tokyo)* 1991;31:336-41.
  44. Rajakulasingam K, Cerullo LJ, Raimondi AJ. Childhood moyamoya syndrome. Postradiation pathogenesis. *Childs Brain* 1979;5:467-75.
  45. Okuno T, Prenskey AL, Gado M. The Moyamoya syndrome associated with irradiation of an optic glioma in children: report of two cases and review of the literature. *Pediatr Neurol* 1985;1:311-6.
  46. Bitzer M, Topka H. Progressive cerebral occlusive disease after radiation therapy. *Stroke* 1995; 26:131-6.
  47. Kestle JR, Hoffman HJ, Mock AR. Moyamoya phenomenon after radiation for optic glioma. *J Neurosurg* 1993; 79: 32-5.
  48. Brant-Zawadzki M, Anderson M, De Armond SJ. Radiation-induced large intracranial vessel occlusive vasculopathy. *AJR Am J Roentgenol* 1980;134:51-5.
  49. Rudoltz MS, Regine WF, Langston JW. Multiple causes of Cerebrovascular events in children with tumors of the parasellar region. *J Neurooncol* 1998;37:251-261.
  50. Mori K, Takeuchi J, Ishikawa M, et al. Occlusive arteriopathy and brain tumor. *J Neurosurg* 1978;49: 22-35.
  51. Amro A, Schultz H. Moyamoya vasculopathy after cranial irradiation-a case report. *Acta Oncol* 1995;34: 261-3.
  52. Hirata Y, Matsukado Y, Mihara Y, et al. Occlusion of the internal carotid artery after radiation therapy for the chiasmal lesion. *Acta Neurochir (Wien)* 1985;74:141-7.
  53. Kitano S, Sakamoto H, Fujitani K, Kobayashi Y. Moyamoya disease associated with a brain stem glioma. *Childs Nerv Syst* 2000;16:251-5.
  54. Hug EB, Muentner MW, Archambeau JO. Conformal proton radiation therapy for pediatric low-grade astrocytomas. *Strahlenther Onkol* 2002;178:10-17.
  55. Kondoh T, Morishita A, Kamei M. Moyamoya syndrome after prophylactic cranial irradiation for acute lymphocytic leukemia. *Pediatr Neurosurg* 2003;39:264-9.
  56. Serdaroglu A, Simsek F, Gucuyener K. Moyamoya syndrome after radiation therapy for optic pathway glioma: case report. *J Child Neurol* 2000;15:765-7.
  57. Sinsawaiwong S, Phanthumchinda K. Progressive cerebral occlusive disease after hypothalamic astrocytoma radiation therapy. *J Med Assoc Thai* 1997;80:338-42.
  58. Yamamoto T, Koeda T. [Moyamoya-like vascular changes 6 years after radiation therapy in a boy]. *No To Hattatsu* 1996;28:525-7.
  59. Darmody WR, Thomas LM, Gurdjian ES. Postirradiation vascular insufficiency syndrome. Case report. *Neurology* 1967;17:1190-2.
  60. Taveras JM. Multiple progressive intracranial arterial occlusions: a syndrome of children and young adults. *AJR Am J Roentgenol* 1969; 106:235-68.
  61. Hilal SK, Solomon GE, Gold AP, Carter S. Primary cerebral arterial occlusive disease in children. II. Neurocutaneous syndromes. *Radiology* 1971;99:87-94.
  62. Debrun G, Lacour P. A new case of moyamoya disease associated with several intracavernous aneurysms. *Neuroradiology* 1974;7: 277-82.
  63. Painter MJ, Chutorian AM, Hilal SK. Cerebrovasculopathy following irradiation in childhood. *Neurology* 1975; 25: 189-94.
  64. Montanera W, Marotta TR, terBrugge KG. Cerebral arteriovenous malformations associated with moyamoya phenomenon. *AJNR Am J Neuroradiol* 1990; 11: 1153-6.
  65. Ono K, Fujimoto T, Komatsu K. [Case of occlusion of the circle of Willis associated with the growth of abnormal vascular networks at the base of the brain; its relation to the pathogenesis of so-called "moyamoya" disease]. *No To Shinkei* 1977;29:37-43.
  66. Kyo K, Kirino Y, Sakaki T. Therapeutic irradiation of brain tumor and cerebrovasculopathy. *No Shinkei Geka* 1989; 17:163-70.
  67. Beyer RA, Paden P, Sobel DF, Flynn FG. Moyamoya pattern of vascular occlusion after radiotherapy for glioma of the optic chiasm. *Neurology* 1986;36:1173-8.
  68. Mitchell WG, Fishman LS, Miller JH. Stroke as a late sequela of cranial irradiation for childhood brain tumors. *J Child Neurol* 1991;6: 128-33.
  69. Fajardo LF, Berthrong M. Vascular lesions following radiation. *Pathol Annu* 1988;23:297-330.
  70. Omura M, Aida N, Sekido K. Large intracranial vessel occlusive vasculopathy after radiation therapy in children: clinical features and usefulness of magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 1997; 38: 241-9.
  71. NJ Ullrich, R. Robertson, DD Kinnamon, RM Scott, MW Kieran, CD Turner, SN Chi, et al. Moyamoya following cranial irradiation for primary brain tumors in children. *Neurology* 2007;68:932-8.
  72. Ken-ichiro Kikuta, Yasushi Takagi, Kazuhiko Nozaki et al. Effects of intravenous anesthesia with propofol on regional cortical blood

- flow and intracranial pressure in surgery for moyamoya disease. *Surgical Neurology* 2007; 68:421-4.
73. Iwama T, Hashimoto N, Yonekawa Y. The relevance of hemodynamic factors to perioperative ischemic complications in childhood moyamoya disease. *Neurosurgery* 1996;38:1120-6.
  74. Sakamoto T, Kawaguchi M, Kurehara K, Kitaguchi K, Furuya H, Karasawa J. Risk factors for neurologic deterioration after revascularization surgery in patients with moyamoya disease. *Anesth Analg* 1997;85:1060-5.
  75. Sato K, Shirane R, Yoshimoto T. Perioperative factors related to the development of ischemic complications in patients with moyamoya disease. *Child's Nerv Syst* 1997;13:68-72.
  76. Abouleish E, Wiggins M, Ali V. Combined spinal and epidural anesthesia for cesarean section in a parturient with moyamoya disease. *Acta Anaesthesiol Scand* 1998; 42:1120-3.
  77. Furuya A, Matsukawa T, Ozaki M, Kumazawa T. Propofol anesthesia for cesarean section successfully managed in a patient with moyamoya disease. *J Clin Anesth* 1998;10:242-5.
  78. Kansha M, Irita K, Takahashi S, Matsushima T. Anesthetic management of children with moyamoya disease. *Clin Neurol Neurosurg* 1997;99(Suppl 2):S110-3.
  79. Kurehara K, Ohnishi H, Touho H, Furuya H, Okuda T. Cortical blood flow response to hypercapnia during anaesthesia in moyamoya disease. *Can J Anaesth* 1993; 40:709-13.
  80. Miyamoto S, Nagata I, Hashimoto N, Kikuchi H. Direct anastomotic bypass for cerebrovascular moyamoya disease. *Neurol Med Chir (Tokyo)* 1998;8 (Suppl):294-6.
  81. Matta BF, Heath KJ, Tipping K, Summors AC. Direct cerebral vasodilatory effects of sevoflurane and isoflurane. *Anesthesiology* 1999 ; 91:677- 80.
  82. AM Hogan, FJ Kirkham, EB Isaacs, AM Wade et al. Intellectual decline in children with moyamoya and sickle cell anaemia. *Developmental Medicine & Child Neurology* 2005, 47: 824-9.
  83. Shinya Sato, Reizo Shirane, Shin Maruoka et al. Evaluation of Neuronal Loss in Adult Moyamoya Disease by 123I-Iomazenil SPECT. *Surg Neurol* 1999; 51:158-63.