Review Article

MOYAMOYA DISEASE
AN UNCOMMON CAUSE OF YOUNG STROKE

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Introduction

Moyamoya disease is a chronic cerebral vasculopathy first described in 1957 by Takeuchi and Shimizu[1]. Progressive occlusion of the arteries of the circle of Willis leads to development of the characteristic collateral vessels and these vessels are a network of preexisting normal collaterals that have dilated in parallel to the occlusion of the circle of Willis. Suzuki and Takaku observed that the collateral vessels give the appearance of a puff of smoke on arteriography and anointed the name "moyamoya" (puff of smoke in Japanese) in 1969[2]. Moyamoya involved both intracranial internal carotid arteries and their major branches - the anterior cerebral artery or the middle cerebral artery. The posterior cerebral artery and posterior communicating artery can also be affected in advanced stages. Clinically, both ischemic and hemorrhagic events can occur in this disease. Thus, moyamoya disease has a bimodal incidence. Incidence of moyamoya disease among females is 1.8 times more than that among males and the highest incidence is found in the Asia, especially in Japan (0.35-2.0 cases per 100,000)[2, 3]. In any case of young stroke with undetected cause, searching for intracranial vessels abnormality by doing digital subtraction angiogram can give us more inclusive information like; moyamoya disease. Because, a prompt diagnosis and surgical cerebral revascularization can make the prognosis much better. This study reviewed the literature and present radiological and angiographic features of a young patient, who was diagnosed as moyamoya disease at Dhaka Medical College Hospital (DMCH).

Aetiology

Aetiology of the disease is still unknown. A genetic mode of inheritance is considered possible cause, because of the higher incidence of the disease in Asia, especially in Japan and the 7%-10% familial occurrence among the Japanese as well as in Caucasians[4,5]. There have been recent reports of increased familial incidence of the disease. In a recent total genome search, a linkage was found between the disease and markers located at 3p24.2-26[6-8]. Another linkage study using markers on chromosome 6, where the HLA gene is located, showed a possible linkage of the marker D6S441 to the disease[9]. DNA typing of HLA also indicates that the disease is probably genetic, also linked to chromosome 17[6, 8].

Pathology and Pathogenesis

The changes in the narrowed vessels are nonspecific. They include hyperplasia and thickening of the intima due to smooth muscle cell proliferation, accompanied by irregularity and duplication of the internal elastic lamina without evidence of an inflammatory process. Changes in the collateral moyamoya vessels probably result from haemodynamic stress on normal vessels[10]. If the disease progresses to occlusion of the stenotic arteries, the Moyamoya vessels disappear[2]. Extra cerebral vasculature can also be affected by the disease[11].

Basic fibroblast growth factor is an angiogenic factor capable of inducing smooth muscle cell proliferation through suppressed apoptosis, has been shown to be selectively present (for unknown reasons) in the intima of the stenotic vessels and is implicated to underlie the pathologic process[12]. Transforming growth factor beta1 (TGF beta 1), a factor involved in angiogenesis and expression of connective tissue genes, was also shown to be elevated in the disease. The cerebrospinal fluid of moyamoya patients contains high levels of inflammatory mediators and the narrowed vessels have an altered reactivity and vessel wall permeability to these substances[13].

What is Moyamoya Syndrome ?

Moyamoya syndrome is a phenomenon caused by an olegemic state similar in presentation like moyamoya disease but caused by various diseases entities, like[14];

a. Genetic disorder :

Neurofibromatosis, Down's syndrome, Turnur syndrome.

b. Hematological disorders :

Sickle cell anemia, Thalessemia, Aplastic anemia.

c. Infectious disease:

Leptospirosis, Tubercular meningitis.

d. Neoplasms :

Craniopharyngioma, Wilm's tumor.

e. Drug abuse:

Phenobarbital.

f. Other:

Polycystic kidney, Irradiation, Trauma

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Clinical Features

There are two age peaks for disease presentation: between 6 and 15 years old and around the fourth decade. Progressive vascular stenosis causes cerebral hypoperfusion and a reduced haemodynamic reserve. These are clinically expressed through ischemic phenomena. Children, more than adults, usually present with cerebral ischemic events, causing transient (or less often, permanent) motor, sensory, cognitive behavioral deficits or endocrine dysfunction, incontinence, migraine-like symptoms and seizures. Transient ischemic attacks are induced by activities associated with hyperventilation, such as crying, running, eating hot dishes, and singing, or by hyperpyrexia. Individuals with this disorder may have disturbed consciousness, speech deficits (usually aphasia), sensory and cognitive impairments, involuntary movements, and vision problems. Ischemic events in adults usually manifest more as an infarction than a TIA[15,16].

A hemorrhagic event is more common in adults. The moyamoya" collaterals, under haemodynamic overload due to compensatory increase in blood flow, are congested and tend to develop aneurysms and pseudoaneurysms[17,18]. In one study, haematoma at basal ganglia was noted in 40% of cases, intraventricular hemorrhage in 30%, thalamic haemorrhage with ventricular rupture in 15% and subcortical haemorrhage in 5% cases[19].

Children with symptomatic moyamoya report a decline in the IQ. So, it is important to start early treatment in children[20]. A few cases of moyamoya disease reported with hypothalamic pituitary dysfunction (hypopituitarism, hypothyroidism)[21].

Angiographic and Clinical Criteria

Angiogram considered the gold standard for diagnosis and follow-up. The classical angiographic changes were first described by Suzuki and Takaku[2] in 1969. These include:

a. Progressive stenosis leading to occlusion of the supraclinoidal internal carotid arteries (usually bilateral) involving also the proximal MCA/ACA (middle/anterior cerebral artery)
b. Numerous dilated perforating vessels in the base of the brain - giving rise to the typical "moyamoya" appearance (smoky).
c. Development of leptomeningeal collaterals (and also - transdural "rete mirabile").
d. Possible progression of occlusion to the posterior communicating artery and posterior cerebral artery with additional collateral supply from branches of the external carotid artery and the ophthalmic system
e. In final stages, the "moyamoya vessels" can completely disappear with cerebral blood supply becoming totally dependent on external carotid artery and vertebro-basilar blood supply.

Now a days Cerebral DSA (digital subtraction angiogram) is done, which is gold standard and this facility also available at Dhaka Medical College Hospital, Bangladesh.

Pathological Criteria

Pathological criteria may be used instead. These are intimal thickening and occlusion or stenosis observed around the intracranial terminal portion of the internal carotid artery and small vessels of conglomerated networks are observed in the pia mater[14].

Imaging

Computed tomography (CT): CT scan is useful to differentiate brain ischemia from brain haemorrhage, in acute stage. However, CT is not definitely diagnostic for moyamoya disease. As a non-invasive imaging, the following magnetic resonance images come in the first line[22].

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA): To avoid the inherent risk of catheter angiography, MRI and MRA are useful and safe, although diagnostic efficacy of MRI and MRA is inferior to that of catheter angiography (Cerebral DSA). Indication of both methods should be balanced in consideration of their merits and risks. Amongst Moyamoya patients, children are good candidates for MRI and MRA[22, 23].

Proton magnetic resonance spectroscopy (MRS): It is an effective method to noninvasively investigate cerebral metabolism.

Electroencephalographic Changes

EEG changes reported in moyamoya include posterior slowing and centrotemporal slow activity. There is sleep spindle depression. A 'rebuilt up' phenomenon after cessation of hyperventilation has been reported. This rebuilt up corresponds to increase in cerebral blood flow in angiography. EEG has sometimes been used in the past for screening but has generally been replaced by magnetic resonance imaging[14].

SPECT

Often nuclear medicine studies such as **SPECT** (single photon emission computerized tomography) are used to demonstrate the decreased blood and oxygen supply to areas of the brain involved (frontal lobes mainly) with moyamoya disease[14].

Treatment

Early diagnosis and treatment are important during childhood as the disease can cause progressive disability, including deterioration in cognitive function[24,25] and because viable cerebral tissue is necessary for reperfusion procedures to succeed. In adults, treatment is aimed at improving cerebral ischemia and preventing repeated

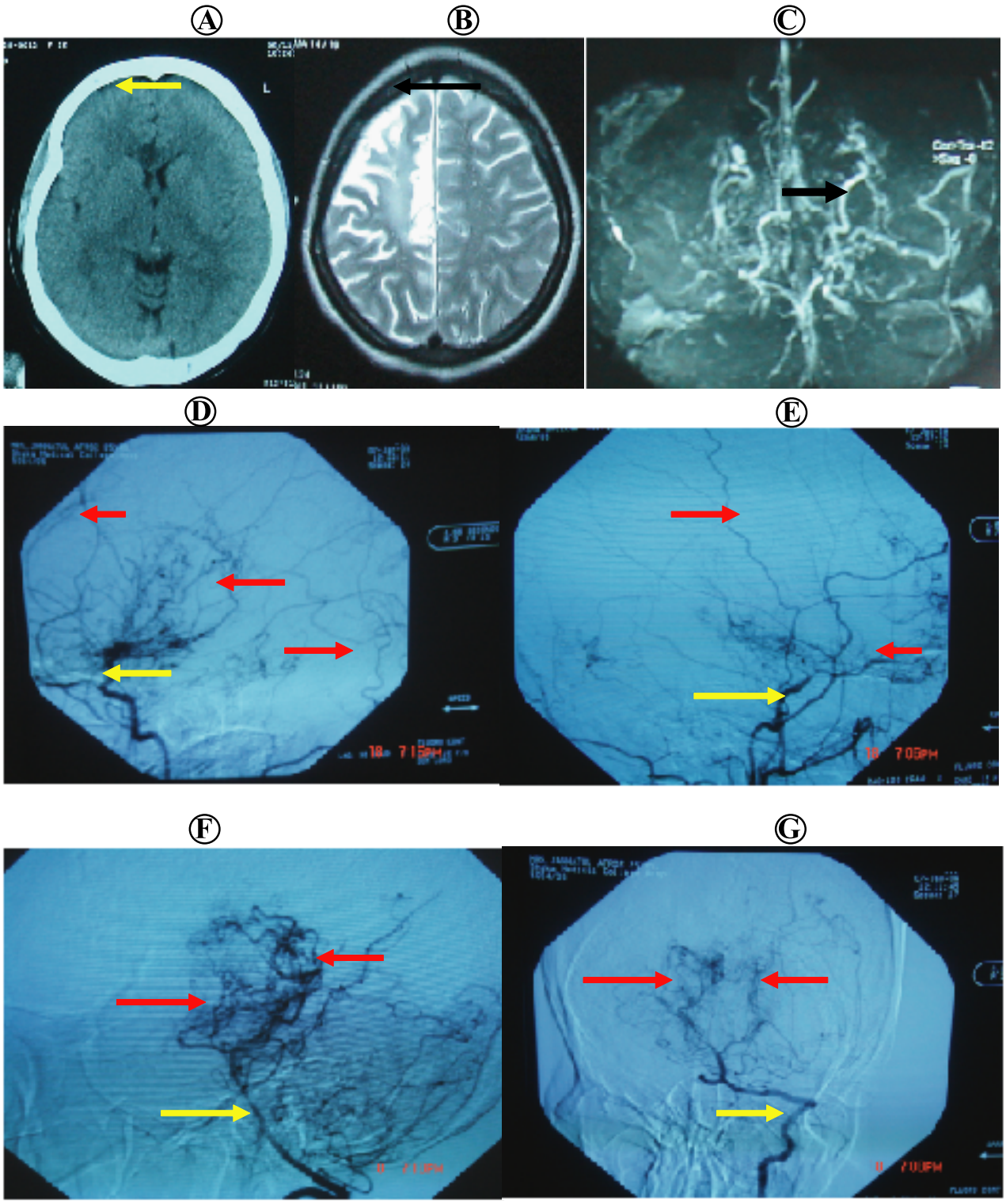

Fig-1: A 25 yrs old lady presented in department of neurology of Dhaka Medical College Hospital with recurrent TIA (transient ischaemic attack) in the form of sudden onset left sided weakness for 4 times within 2 yrs, but about 7 months back she developed Ischaemic stroke with Lt. sided hemiparesis.
(A) CT scan of head revealed infarct in Rt. frontal region (yellow arrow), (B) Axial T2 weighted MRI image shows hyperintence lesion in Rt. frontoparietal region (black arrow), (C) MRA poorly visualised MCAs, ACAs, PCAs and the distal branches are not well seen and numerous collateral vessels in circle of Willis (black arrow), (D) & (E) Cerebral DSA showing discontinuation of Rt. & Lt. ICA at petrous level (yellow arrow). There was multiple Dural & Meningeal vessels (red mark) supplying the MCA &. ACA (Rt. & Lt.) territory giving rise the typical smoky angiographic appearance. (F) & (G) Cerebral DSA of LVA (yellow mark) revealed normal finding with multiple choroidal & meningeeal collaterals with smoky appearance (red mark) compensating the deficient supply. (MCA- middle cerebral artery, ACA- anterior cerebral artery, PCA-posterior cerebral artery, LVA- Lt. vertebral artery, ICA- internal carotid artery, DSA- digital subtraction angiogram.)

intracerebral hemorrhage by reducing the overload on Moyamoya collaterals[3,10]. In children the first line of treatment is pharmacological with antiplatelet therapy or calcium channel blockers, which can ameliorate symptoms but does not halt disease progression. Demonstrating cerebral hypo perfusion or a reduced perfusion reserve are indications for surgical reperfusion procedures, which are eventually performed in about 80% of patients[24, 26-28].

Two basic revascularization procedures are used (separately or in combination):

Direct bypass: mainly superficial temporal artery to MCA. Sometimes used in combined with STA (superficial temporal artery) to ACA bypass. Direct revascularization is more effective in reducing the incidence of hemorrhage in adults[28]. It provides immediate high flow but is difficult to perform in small children due to the small size of the donor and recipient arteries. It is considered less safe than the indirect methods because manipulation of the vessels and the required temporary occlusion of a MCA branch are potentially capable of causing a stroke or reversible ischemic events (reported in about 4.4% and 6.1% of surgeries respectively)[26, 28-30].

Indirect bypass: due to the basic tendency of the ischemic brain to induce the development of collaterals, a direct contact is created between the ischemic brain and another tissue that is the source for the blood supply. The sources, which can be used in various combinations, are:

a) **Dural arterial:** Encephalo-duro-synangiosis - direct application of dura with its blood supply (usually the middle meningeal artery) to a pial surface[31,32].
b) **Muscle:** Encephalo-myo-synangiosis - using a temporalis muscle graft supplied by the deep temporal artery. A relatively large territory can be covered, but not frontal areas (ACA territories are not reachable). Complications include myoelectric activity-induced seizures, generated by muscle contraction and a cosmetic defect in the temporal fossa[33].
c) **Superficial arterial:** Encephalo-arterio-synangiosis - the STA is carefully dissected and brought in contact with the brain through an opening in the cranial vault and the dura[34].
d) **Galea:** Encephalo-galeo-synangiosis - bringing the galea through a burr hole or craniotomy and dural incision in contact with the brain (usually to improve blood supply to ACA territories). It is considered a safe procedure because blood vessels are not manipulated, the site can be chosen so as not to disrupt existing leptomeningeal collaterals, and because of the short operating time, but the territory that can be revascularized is quite limited in size[35].

The disadvantage of indirect revascularization techniques is their delayed efficacy, pending the development of collaterals, a process that can take months. Strokes occurring during this period could be devastating. Still, with direct or indirect procedures, incidence of perioperative cerebral infarction has reached 13%[26,31,35,36].

Prognosis

Without surgery, the majority of individuals with moyamoya disease will experience mental decline and multiple strokes because of the progressive narrowing of arteries. Without treatment, moyamoya disease can be fatal as the result of intracerebral hemorrhage. Rebleeding is common. Mortality increases when rebleeds and generally the prognosis worsen with each rebleed[5,17, 18, 23, 36].

Conclusion

Moyamoya disease is a relatively rare disease with severe morbidity, mortality in both pediatric and adult group. In any case of young stroke with undetected cause, one should think of this[37]. Because, a prompt diagnosis and surgical cerebral revascularization can make the prognosis much better.

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