TIA and Headache in Pediatric Moyamoya Disease

7

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Abstract

This chapter precisely reviews the pathophysiology and clinical features of transient ischemic attack (TIA) and headache in pediatric moyamoya disease. Clinical features of TIA and headache are unique and almost specific for pediatric moyamoya disease. Therefore, the author strongly believes that the understanding of the mechanisms through which TIA and headache occur is quite important to know the moyamoya disease in depth and to perform appropriate surgical treatment for pediatric patients with moyamoya disease.

Keywords

Moyamoya disease · Children · TIA · Headache · Cerebral hemodynamics

7.1 Introduction

Moyamoya disease is known to frequently cause transient neurological symptoms such as transient ischemic attack (TIA) and headache attack in pediatric patients with moyamoya disease [1, 2]. The mechanisms through which these attacks occur are not fully understood, but we strongly believe that early diagnosis and early, appropriate surgical revascularization is the most important factor in preventing the neurological sequelae due to ischemia stroke in children with moyamoya disease.

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In this chapter, we will discuss the mechanisms of TIAs and headache attacks in pediatric moyamoya disease by reviewing in detail previous studies on TIAs and headache attacks in pediatric patients with moyamoya disease.

7.2 Transient Ischemic Attack

7.2.1 Clinical Features and Mechanism

Moyamoya disease is known to cause transient ischemic attacks in many patients, both children and adults [1–3]. Since moyamoya disease essentially begins with a narrowing of the arteries around the terminal portion of the internal carotid artery, many of the neurological symptoms such as hemiparesis and aphasia are often attributed to the cerebral cortex in the frontal and/or temporal lobe. Especially in severe pediatric cases, however, unusual paraparesis, tetraparesis, or loss of consciousness may occur due to dense cerebral ischemia in the bilateral hemispheres [1]. In such cases, we should not misdiagnose it as epilepsy. On the other hand, it is well known that about 30% of patients with moyamoya disease also have stenotic lesions in the posterior cerebral artery (PCA) [4–9]. Disease progression in PCA has been reported to occur up to 15 years after surgical revascularization [10]. Because the PCA is a crucial source of collateral circulation in moyamoya disease, the involvement of PCA often causes neurological symptoms originating from not only the occipital lobe but also the adjacent parietal and posterior temporal lobes [7, 11]. The former includes visual symptoms such as homonymous hemianopsia, while the latter includes sensory aphasia and the numbness of the contralateral face and extremities.

The mechanism by which TIA occurs in moyamoya disease has not been specified. However, it is well known that cerebral hemodynamics is moderately impaired in pediatric moyamoya patients with TIA, but is markedly disturbed in them with ischemic stroke [12]. In addition, many of the infarcts are localized in the MCA-ACA or MCA-PCA watershed zone when TIA progresses to ischemic stroke (Fig. 7.1). These facts strongly suggest that hemodynamic ischemia is more likely involved in the occurrence of TIA than artery-to-artery embolism. This speculation is supported by the fact that the efficacy of antiplatelets is still controversial to prevent TIA and ischemic stroke [13, 14].

Clinical presentation of TIA in pediatric moyamoya disease is highly specific. It is widely known that TIA readily occurs after hyperventilation, such as crying or blowing a whistle or harmonica. However, there are almost no reports proving that TIA occurs after hyperventilation in adult cases of moyamoya disease, which suggests that the mechanism through which TIA occurs may differ between pediatric and adult cases. Previously, there are excellent reports on the mechanism of TIA in pediatric cases. Thus, it was already reported by several investigators in the 1970s, soon after the discovery of this disease, that hyperventilation-induced hypocapnia more distinctly reduced cerebral blood flow in patients with moyamoya disease than in healthy controls. It has also been reported that hypercapnia due to CO_2 loading causes little or no change in cerebral blood flow, or leads to an increase in cerebral

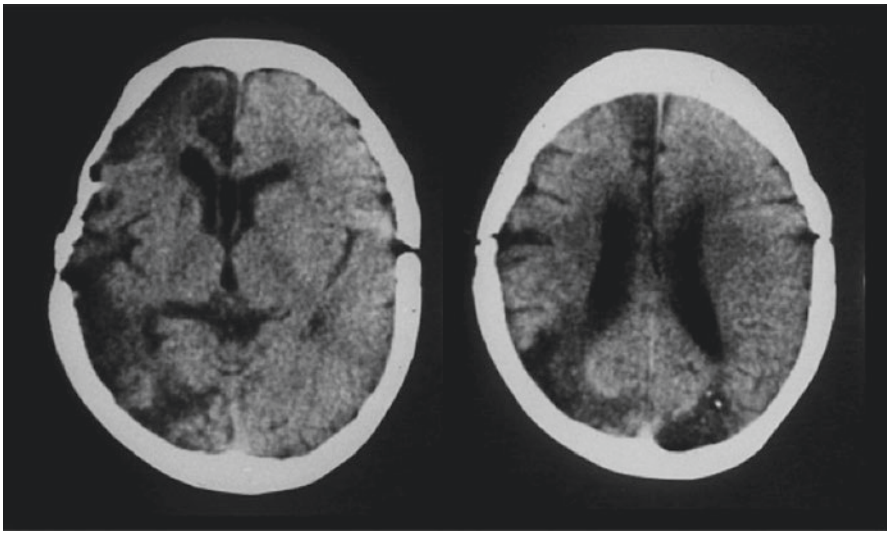

Fig. 7.1 Typical finding of plain CT scan in a 8-year-old boy who developed ischemic stroke. Note that cerebral infarction is mainly located in the borderzone between the MCA and ACA territories or between the MCA and PCA territories

blood flow in the temporo-occipital area but not in the frontal area [15–18]. Surgical revascularization improves the response of cerebral blood flow to hypercapnia [15]. At this time, Takeuchi et al. (1983) already hypothesized that *"a decrease in cerebral perfusion pressure may induce a maximally dilated state of the peripheral arterioles, leading to a loss of response to hypercapnia and an excessive reaction to hypocapnia*" and "*the pathophysiology may be most prominent in the frontal lobe in moyamoya disease*" (author's translation). These speculations are still true even in today's world where measurement techniques of cerebral blood flow and metabolism have advanced dramatically, and the author believes that the depth of the thinking of researchers at that time is extraordinary [18]. Then, Karasawa et al. (1986) precisely evaluated the findings on cerebral angiography during hypercapnia/hypocapnia. As the results, hypocapnia led to a decrease in arterial diameter in the arteries of the brain surface and in the moyamoya vessels of the basal ganglia. This change was more pronounced in the moyamoya vessels of the basal ganglia. Contrast opacification was also reduced in the MCA-ACA watershed zone [15]. Similar results have been reported by Takahashi et al. (1985) [19].

Specific response to hyperventilation in pediatric moyamoya disease has been also studied in the field of electrophysiology. Hyperventilation is known to induce synchronous slow waves on EEG in healthy children, which is observed in almost all parts of the brain and disappears with the cessation of hyperventilation. This phenomenon is called as "build up" phenomenon. In pediatric moyamoya disease, however, a few minutes after the build up disappears after hyperventilation, non-synchronous slow waves with higher amplitude occur, which is completely different from the build up phenomenon. This phenomenon, called re-build up phenomenon,

is very specific to childhood moyamoya disease, and does not occur in adults with moyamoya disease (Fig. 7.2a). Because TIA has been often observed during re-build up phenomenon in pediatric moyamoya patients, several investigators have studied its pathophysiology using a variety of modalities to elucidate the mechanisms through which TIA develops in pediatric moyamoya disease [20]. Using ^{15}O positron emission tomography (PET), Kameyama et al. (1986) serially measured cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) before and after hyperventilation in three pediatric cases of moyamoya disease. As the results, both CBF and $CMRO_2$ significantly decreased in response to 3-min hyperventilation. A decrease in $CMRO_2$ was more pronounced than that in CBF. More interestingly, continuous measurement of PaO_2 and $PaCO_2$ revealed that hyperventilation led to an increase in PaO_2 as well as a decrease in $PaCO_2$ during

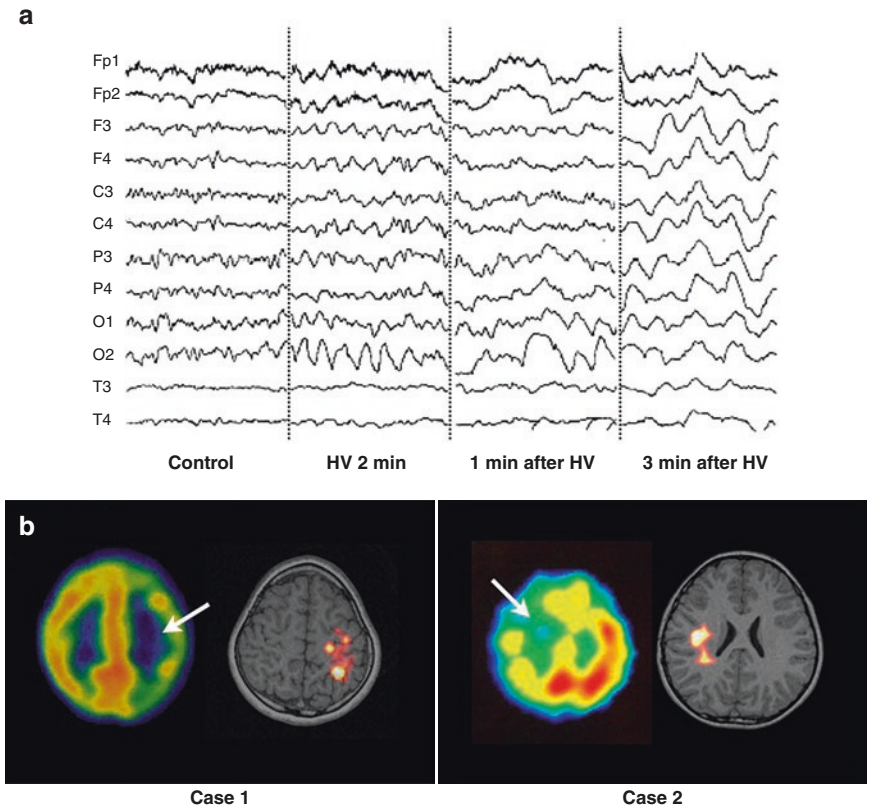

Fig. 7.2 (**a**) Typical EEG finding in a 4-year-old girl demonstrating the build up phenomenon during hyperventilation (HV) and the re-build up phenomenon after the cessation of HV. (**b**) Representative findings of acetazolamide-loaded cerebral blood flow map on SPECT and MEG in a 8-year-old girl (*left*) and a 12-year-old boy (*right*). Note a strong correlation between the area with impaired reactivity to acetazolamide (arrows) and the localization of original current dipoles of re-build up phenomenon

hyperventilation, and then the cessation of hyperventilation induced a rapid fall of PaO_2 as well as a gradual recovery of $PaCO_2$. They speculated that re-build up phenomenon may occur through not only ischemic hypoxia but also hypoxic hypoxia probably because of respiratory inhibition in response to PaO_2 elevation during hyperventilation [21]. Using ^{133}xenon inhalation method and single photon emission tomography (SPECT), Isobe and co-workers measured CBF before and after hyperventilation in 11 pediatric patients with moyamoya disease, and found a strong correlation between the areas where the re-build up phenomenon emerges on EEG and the areas where CBF markedly decreases after hyperventilation [22, 23]. Kuroda et al. (1995) reported that the re-build up phenomenon originated from the cerebral cortex where cerebrovascular reactivity to acetazolamide is severely impaired and disappeared after effective surgical revascularization [24]. In addition, they first applied near-infrared spectroscopy (NIRS) into this research field and continuously measured cerebral oxygenation state before and after hyperventilation in two pediatric patients. NIRS is known capable to monitor the changes in the concentrations of oxidized hemoglobin (oxy-Hb), deoxidized hemoglobin (deoxy-Hb), and total Hb (tHb) through the detectors put on the scalp noninvasively and to have a good time resolution (one datum per second). As the results, hyperventilation promptly decreased the concentrations of oxy-Hb and tHb in the frontal area on NIRS, causing the build up phenomenon. When the hyperventilation was stopped, the build up phenomenon disappeared, but the concentrations of oxy-Hb and tHb remained lower than the control value. Then, the concentration of oxy-Hb further decreased and the concentration of deoxy-Hb started to increase, leading to the occurrence of the re-build up phenomenon. Thereafter, the re-build up phenomenon disappeared as the parameters on NIRS gradually recovered to their control values. The results strongly suggest that the involved brain is exposed to more severe hypoxia after the cessation of hyperventilation than during hyperventilation in pediatric moyamoya disease [25]. The findings on NIRS correlates very well with those on ^{15}O PET reported by Kameyama et al. [21]. Subsequently, Qiao et al. (2003) first analyzed the spontaneous magnetic brain activity on a whole-head magnetoencephalography (MEG) system during and after hyperventilation in four pediatric patients with moyamoya disease. They found that the original current dipoles of the re-build up slow waves were mainly originating from the deep cortical sulci in the area where cerebrovascular reserve was disturbed on SPECT (Fig. 7.2b) [26]. However, no subsequent studies have been reported to elucidate the mechanism of the re-build up phenomenon in moyamoya disease, probably because the risk of TIA and ischemic stroke due to hyperventilation has reduced the availability of EEG itself.

7.2.2 Natural Course of TIA

Many pediatric patients have been reported to develop ischemic stroke after they repeated TIAs. In fact, Maki et al. (1976) reported that 8 of 24 pediatric patients had a poor outcome. Of these, one patient died of acute subdural hematoma, two had a severe motor and mental deficits, and the other five required special education. They

concluded that their functional outcome was “good” in one-thirds, “borderline” in one-third, and “poor” in one-thirds, and that repeated TIAs followed by ischemic stroke was one of the determinants to predict poor outcome [27]. Kurokawa et al. also reported that the prevalence of patients with mild-to-severe disabilities increased up to about 50% with duration of illness [28]. Such a transition from TIA to ischemic stroke may result from severe cerebral ischemia since the onset of the disease as well as from a stepwise deterioration of cerebral hemodynamics in response to a disease progression.

On the other hand, however, several reports have shown that the frequency of TIAs gradually declines through adolescence in patients with repeated TIAs only and no conversion to ischemic stroke [28–30]. In fact, Kurokawa et al. (1985) reported that TIAs frequently occurred during the first 4 years after the onset and the frequency decreased thereafter [28]. This phenomenon may be related to the fact that the incidence of moyamoya disease is high in children between the ages of 5 and 15 years, but is much lower in young adults around the age of 20 years. Although the mechanism is not entirely understood, the author speculates that it is closely related to the fact that cerebral blood flow in children drastically changes with growth. In children, cerebral blood flow is reported to greatly vary with growth; Using the ^{133}xenon inhalation method, Takeuchi et al. (1983) measured the mean CBF value in healthy children and found that the mean value of CBF was 67.7 ml/min/100 g in healthy children (7–17 years of age), but was 53.6 ml/min/100 g of CBF in healthy adults (22–67 years old). They also found a more pronounced decrease in CBF with growth in children than in adults [18]. Subsequently, Ogawa et al. (1990) also measured CBF in healthy children and adults, and reported that CBF was higher than 100 ml/min/100 g in infants, but rapidly declined by age of 20 years followed by a gradual decline thereafter. According to their data, the changes in CBF showed a nonlinear curve as follows [31]:

$$\mathrm{Y} = 146.5 - 58.4 \log \mathrm{X}, \text{where X is the age} \left(P < 0.01, \mathrm{R} = -0.903 \right).$$

Kuroda et al. (1993) also reported a negative correlation between CBF and age in healthy children. More interestingly, they found that once surgical revascularization improved CBF in children with moyamoya disease, CBF gradually declined with growth, just as it does in healthy children [12]. These dynamic profiles of CBF in children are most likely linked to those of brain metabolism. Thus, Kennedy and Sokoloff (1957) showed that brain oxygen utilization was about 1.3 times higher in children than in adults [32]. Chugani et al. (1987) measured cerebral metabolic rate for glucose (CMRGlc) using PET, and concluded that the value was very low at birth, increased by 3 to 4 years old, and continued at high levels until 9 years old, when the value started to decrease, reaching adult value by the latter part of the second decade [33].

Based on these observations, I speculate the mechanism through which TIA decreases in frequency with growth as follows: Children with severely impaired cerebral hemodynamics since the onset of the disease repeat TIAs and develop ischemic stroke within several years, leading to a poor functional outcome. On the other

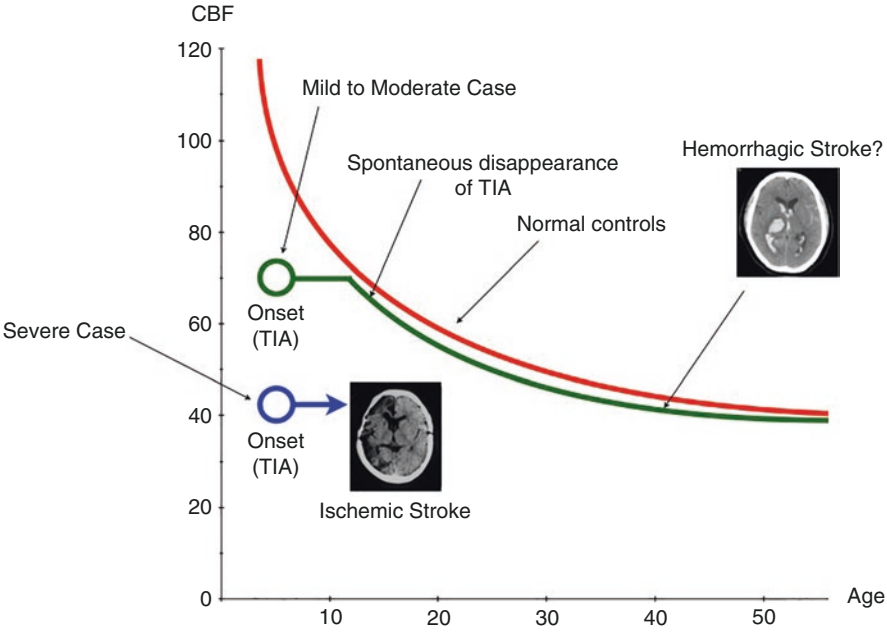

Fig. 7.3 A diagram demonstrating Kuroda's theory about the relationship between the age and cerebral blood flow (CBF) in healthy children (*red*) and moyamoya patients with severe (*blue*) and mild-to-moderate CBF decrease (*green*). See the text in detail

hand, children with mild-to-moderate impairment of cerebral hemodynamics at the onset will grow up with repeated TIAs. Because normal CBF levels gradually decline with growth, it is likely that patients' CBF levels will not differ much from healthy controls at some point in time and the frequency of TIAs may gradually decrease and even disappear (Fig. 7.3). So, it is not surprising that there are not a small number of cases of repeated mild TIAs in childhood that were not diagnosed as moyamoya disease in the hospital, but in time their TIAs disappeared and they became adults. Some of them may go their entire lives without experiencing any stroke. But, some others may develop the rupture of dilated, fragile moyamoya vessels due to a long-lasting hemodynamic stress, causing hemorrhagic stroke at around the age of 40 years (Fig. 7.3). In fact, a recent cohort study has found that adult moyamoya disease that may have occurred in childhood was associated with a higher incidence of hemorrhagic stroke than adult-onset moyamoya disease, with a higher incidence of lenticulostriate and choroidal channels as spontaneous collaterals [34].

7.3 Headache Attack

As with TIA, the clinical presentation of headache attacks in pediatric moyamoya disease is very different from that of adults. The occurrence of headache attacks in pediatric moyamoya disease appears to have been recognized soon after the disease

was discovered, but scientific analysis did not start to be done until the 1990s. Since then, several case reports have pointed out that children with moyamoya disease develop migraine-like headaches [35–38].

For these two decades, there are several reports on headache attacks with relatively large cohorts [39–42]. According to these reports, the frequency of pediatric patients with headache attacks ranges from 22 to 38% of all pediatric patients. Their ages are distributed throughout childhood. There is no difference in age or gender between children with and without headache attacks [39–42]. Some children have recurrent headaches alone, while others have recurrent headaches and TIAs. In some patients, TIAs may occur with headache attacks [42].

Typically, their headache resembles migraine without aura and is associated with nausea and/or vomiting in one-thirds of them. Their headache usually occurs in the morning, especially when they woke up [39, 42]. Their headache attacks are often severe, because most of them cannot go to their school or kindergarten. The frequency of headache attacks was every day, every week, or every month in most of the cases. All of them repeat severe headaches in the unilateral or bilateral frontal and/or temporal area [39, 40]. Symptomatic drugs are not effective to relieve them [42]. Therefore, it should be stated that headache attacks in pediatric moyamoya disease are quite frequent and have a significant impact on daily life, including school [39]. Headache attacks usually resolve spontaneously in about 2–5 h [39, 40]. As a result, many pediatric patients complain of a headache in the morning and miss school but feel fine by noon, so their mothers who do not know that moyamoya disease is the cause may even suspect that their child is skipping school by pretending to have a headache.

These observations strongly suggest that the mechanisms of TIA and headache attack development are in very close proximity. Suzuki's angiographical stage is more advanced in pediatric patients with headache attacks than in those without [39]. Using cold xenon CT, Okada et al. (2012) measured CBF in the MCA territory, but found no significant difference in CBF between headache group and non-headache group. In pediatric patients, cerebrovascular reactivity (CVR) to acetazolamide was lower in headache group than in non-headache group, although statistical significance was borderline probably due to a small sample size [41]. Subsequently, however, Kawabori et al. (2012) reported that a decreased CBF and impaired CVR to acetazolamide were significant predictors for the occurrence of headache attacks. More importantly, there was a very strong correlation between the localization of headache and the area with impaired cerebral hemodynamics [39].

Several investigators have also evaluated the therapeutic effect of surgical revascularization on headache attacks in pediatric moyamoya disease. Thus, headache remained in 25 to 63% of patients after EDAS surgery [40, 42]. At least a 2-month period is required to resolve headaches after EDAS [43]. On the other hand, Okada et al. (2012) reported that headache markedly improved in 23 of 25 patients just after STA-MCA double anastomosis and advocated the superiority of direct bypass over EDAS in treating headache attacks. In their surgical procedures, two branches of the STA were anastomosed to two cortical branches of the MCA feeding to the

frontal and temporal lobe, respectively [41]. Kawabori et al. (2013) demonstrated that headache completely disappeared in all patients within 2 weeks after STA-MCA single or double anastomosis and encephaloduro-myo-arterio-pericranial synangiosis (EDMAPS). They also anastomosed one of the STA branches to the frontal branch of the MCA. On postoperative cerebral angiography, surgical collaterals widely provided collateral blood flow to the operated hemispheres through direct and indirect bypass, including the area with a headache before surgery. Postoperative CBF study also revealed that both CBF and CVR significantly improved in the operated hemispheres, including the area where patients repeated headache before surgery [39].

These facts strongly suggest that persistent cerebral ischemia is closely involved in the development of migraine-like headache attacks in pediatric moyamoya disease [39, 41]. As mentioned above, most headache attacks occur primarily in the frontal region. However, EDAS primarily improves cerebral hemodynamics only in the parietal region, so a significant number of patients may still experience headache attacks even after EDAS. In addition, indirect bypass procedures such as EDAS require several months to complete angiogenesis between the donor tissues and brain surface (see Chap. 18), which may delay the resolution of headache after EDAS. On the other hand, STA-MCA anastomosis with or without indirect bypass has a great potential to improve cerebral hemodynamics in the frontal lobe just after surgery by anastomosing the STA branch to the frontal branch of the MCA. The fact may be able to explain the reason why headache attacks quickly disappear after STA-MCA anastomosis targeted to the frontal lobe [39, 41]. More scientifically, Olesen et al. (1993) reported three patients who had repeated migraine episodes because of severe stenosis or occlusion of the internal carotid artery. All of them had reduced cerebral blood flow in the involved hemispheres. They hypothesized that borderline ischemia may increase the risk of spreading cortical depression and lower the threshold for developing migraine, thereby inducing aura with or without headaches [44]. Their hypothesis is extremely interesting in considering the mechanism of headache attacks in pediatric moyamoya disease.

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