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Pediatric Issue

Moyamoya Syndrome : A Window of Moyamoya Disease

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Moyamoya-like vasculopathy develops in association with various systemic diseases and conditions, which is termed moyamoya syndrome. Relatively common diseases and conditions are related to moyamoya syndrome, including neurofibromatosis type 1, Down syndrome, thyroid disease, and cranial irradiation. Moyamoya syndrome shares phenotypical characteristics with idiopathic moyamoya disease. However, they differ in other details, including clinical presentations, natural history, and treatment considerations. The study of moyamoya syndrome can provide clinicians and researchers with valuable knowledge and insight. Although it is infrequently encountered in clinical practice, moyamoya-like vasculopathy can severely complicate outcomes for patients with various underlying diseases when the clinician fails to expect or diagnose moyamoya syndrome development. Furthermore, moyamoya syndrome could be used as a doorway to more enigmatic moyamoya disease in research. More comprehensive survey and investigation are required to uncover the secrets of all the moyamoya-like phenomena.

Key Words : Moyamoya syndrome · Neurofibromatosis · Down syndrome · Thyroid disease · Radiation.

INTRODUCTION

Moyamoya disease is characterized by progressive stenosis and occlusions of distal internal carotid arteries (ICAs) and their major branches. The vascular stenosis/occlusion is accompanied by the growth of small collateral vessels in the bottom of cerebrum, hence the name came 'moyamoya' (which describes a puff of smoke in Japanese)[27]. The disease usually involves bilateral hemispheres, although in some patients, the arterial stenosis/occlusion occurs in only one side, which is called unilateral (probable) moyamoya disease. The more specific definition of moyamoya disease is 'an idiopathic occlusion of bilateral vessels of the circle of Willis'[41]. This consensus definition entails the most crucial characteristics of the disease, i.e., the specific location (the circle of Willis), the pathophysiological nature (vascular occlusion), bilateral involvement, and most importantly, the etiology (idiopathic). As stated in the definition, the moyamoya disease etiology is unknown to date. There is an obvious familial tendency, in which there is a 6−12% risk of developing the disease if a person has a first-degree relative with moyamoya disease[25,44]. There is also an ethnic predilection for Asian populations, especially for people with Korean and Japanese ancestry. The moyamoya disease incidences in East Asia is about 10 times that of Western countries[54]. Genetic linkage studies revealed putative chromosomal locations linked to moyamoya disease[14,16,31,53]. The recent discovery of a strong disease-associated genetic locus in the ring finger protein (RNF) 213 gene supports the presence of weak areas in human genome that lead to moyamoya susceptibility[22,32]. Apart from the genetic hypotheses, various environmental factors have been proposed as etiological factors of moyamoya disease. They include infectious agents, immunological responses with cellular components and autoantibodies, and hemodynamic stress to specific vascular loci, just to name a few[36,42,47,52]. Nonetheless, the causal relationships for this enigmatic disease remain elusive and the entire picture of the genetic/environmental contributions to moyamoya pathogenesis is still awaiting more investigation and elaboration.

Typical angiographic findings of moyamoya disease, the stenosis/occlusion of distal ICA and development of basal collaterals are not specific to the disease. Hence, we will use a provisional term, moyamoya-like vasculopathy to denote the phenomenon. Sometimes, moyamoya-like vasculopathy develops in patients with other well-characterized diseases or syndromes[41]. In these patients, the condition is called moyamoya syndrome rather than moyamoya disease because the underlying disease/syndrome may be associated with cerebral vasculopathy pathogenesis. There are many types of moyamoya-associated diseases

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and conditions (Table 1). However, clinicians have noticed that some diseases have more frequent associations with moyamoya-like vasculopathy. These include neurofibromatosis type 1 (NF-1), Down syndrome, Grave's disease, therapeutic irradiation, sickle cell anemia, and others.

Delving into the moyamoya syndrome has two important meanings. First, moyamoya-type vasculopathy, i.e., the location-specific stenosis/occlusion of vessels around the distal internal carotid arteries, is a disease-defining feature; however, it should be considered a phenomenon in itself if devoid of etiological connotations. In other words, (idiopathic) moyamoya disease and moyamoya syndrome share a phenotype of cerebral vasculopathy, at least to some degree. If they have a similar phenotype, then they may have a common pathogenesis in vascular occlusion and collateral vessel development. Many of the moyamoya-associated conditions have well-recognized etiologies and pathogenic mechanisms. Therefore, researching individual moyamoya syndrome can open up a novel avenue in the quest for describing the moyamoya disease etiology and pathogenetic mechanisms. For example, NF-1 is caused by germline haploinsufficiency of the NF1 allele, and its protein is a key component of the RAS-RAF signaling pathways[20]. NF1-haploinsufficient mice, which display some hallmarks of human NF-1, have been widely used in research fields[17]. Because the lack of a pertinent animal model is a major obstacle in moyamoya disease research, moyamoya syndrome with NF-1 may serve as a good substitute.

Table 1. Moyamoya syndrome-associated diseases and conditions

Relatively common moyamoya syndrome
Neurofibromatosis type 1
Down syndrome
Thyroid disease
Cranial irradiation
Sickle cell anemia
Extremely rare moyamoya syndrome
Systemic lupus erythematosus
Turner syndrome
Noonan syndrome
Alagille syndrome

Second, moyamoya-like vasculopathy, which produces symptoms and stroke in certain occasions, is a serious complication of individual moyamoya-associated diseases and syndromes. Many of the moyamoya-associated conditions are uncommon entities and usually only a small fraction of the patients develop moyamoya syndrome during the course of the underlying illness. Nonetheless, failure to diagnose moyamoya syndrome in these patients in time may lead to severe stroke and neurological deficits, which could be prevented with appropriate treatments. Frequently, the apparent clinical features of an underlying disease make timely diagnoses of moyamoya syndrome difficult. For instance, headache and transient ischemic attack (TIA), the most frequent symptoms of moyamoya syndrome, may be difficult to detect in patients with Down syndrome[18]. Therefore, clinicians managing these patients should have knowledge of moyamoya syndrome and make a screening plan for selected patient groups.

In this article, several major diseases and syndromes frequently associated with moyamoya syndrome are briefly reviewed, especially with regard to their clinical characteristics and pathogenetic mechanisms.

NF-1

NF-1, also known as von-Recklinghausen disease, is a syndrome caused by a germline loss of one NF1 gene allele. NF-1 is an autosomal dominant disorder with a relatively high incidence in the population, affecting approximately 1 in every 2500 to 3000 children[20]. NF-1 involves multiple organs, including the brain, peripheral nerves, eyes, skin, and bones. Common cerebral manifestations in NF-1 patients include optic glioma, macrocephaly, focal areas of signal intensity on magnetic resonance images (MRI), and learning and cognitive disabilities. NF-1 occasionally causes systemic vasculopathy such as renal arterial stenosis, and some patients develop cerebral vasculopathy (Fig. 1)[12,30]. Cerebral vasculopathy encompasses stenosis/

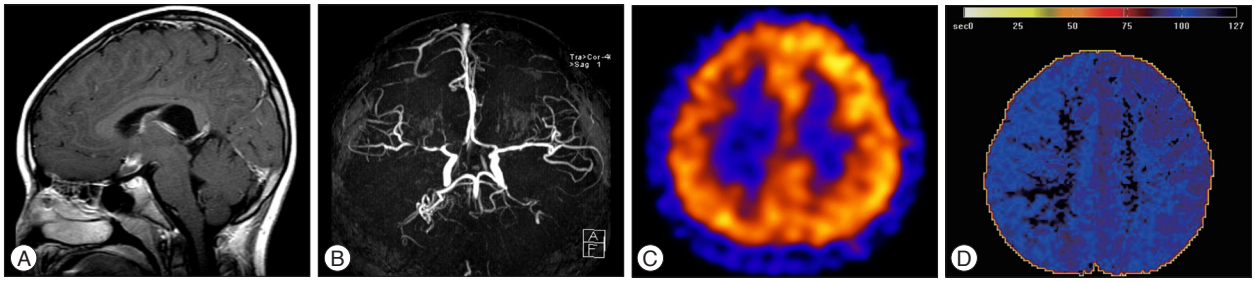

Fig. 1. Images of a boy with neurofibromatosis type 1. A : Magnetic resonance image (MRI) taken at age 7 revealed a thickened optic chiasm with gadolinium enhancement, suggesting the presence of an optic glioma. The boy experienced symptomatic progression of the optic glioma and received cranial irradiation (50.4 Gy) for treatment at age 9. B : Magnetic resonance angiography (MRA) was taken 4 years after the radiation therapy. Note the luminal narrowing of bilateral middle cerebral arteries (right side more severe) and the invisible horizontal portion of the right anterior cerebral artery. C : A markedly decreased vascular reserve in the right hemisphere was shown after infusion of diamox in single photon emission computed tomography. D : A delayed time-to-peak in the right hemisphere was also observed in a perfusion MRI. At that time, the patient was asymptomatic and no treatment was recommended. One year later, the patient began to complain of morning headaches, with increasing intensity over time. Encephaloduroarteriosynangiosis was performed on the right side. After surgery, the patient was free of headaches.

Table 2. Summary of the large-scale studies on the prevalence of moyamoya syndrome in NF-1 patients

	Ghosh et al.[12]	Rea et al.[39]	Cairns and North[5]	Rosser et al.[40]
NF-1 patients	398	419	698	353
Patient with brain MRI	312 (78%)	266 (63%)	144 (21%)	316 (90%)
Patient with brain MRA/angiogram	143 (46%)	35 (13%)	Only for patients with vasculopathy	Only for patients with vasculopathy
Cerebral vasculopathy	15 (4.8%)	17 (6.4%)	7 (4.9%)	8 (2.5%)
Median age at diagnosis of vasculopathy	11.7 yr	5.3 yr	6.0 yr	7.3 yr (mean)
Presence of optic glioma	7	13	5	NA
Cranial irradiation	0	0	Excluded from the study	NA
Moyamoya-like vasculopathy	7	13	1	2
Unilateral*	5	12	1	1
Symptomatic*	0	6	1	1
Focal neurological deficit*	0	6	1	1
Progression*	2	6	0	1
Revascularization surgery*	1	6	0	2

*Denotes the number of patients with each characteristic among the patients with moyamoya-like vasculopathy

occlusion and aneurysmal dilatation. In children, the stenosis/occlusion type predominates over the aneurysmal dilataion type[45].

There are 4 large-sized studies that reported the prevalence of cerebral vasculopathy in NF-1 patients (Table 2)[5,12,39,40]. Rosser et al.[40] reported the smallest prevalence value (2.5%) and Rea et al.[39] suggested the largest prevalence rate (6.4%). The differences may result from the various proportions of patients who were administered brain MRI and, more importantly, brain magnetic resonance angiography (MRA) for screening examinations in each study. Taking these differences in mind, approximately 1 in 20 NF-1 patients (~5%) develops cerebral vasculopathy. Not all stenosis/occlusion type cerebral vasculopathy cases are moyamoya-like in NF-1 patients. Some patients have typical moyamoya-type stenoses; however, others display diffuse narrowing of the petrous or moyamoya-like ICA or stenosis of the distal middle cerebral artery without moyamoya vessels. A small portion of these patients also have aneurysmal dilation in their major vessels[5,39]. The proportion of moyamoya-like vasculopathy is quite variable in the published studies. Rea et al.[39] reported that 13 of their 17 observed patients had cerebral vasculopathy and Ghosh et al.[12] found that 7 of their 15 observed patients exhibited moyamoya-like vasculopathy. In a study by Cairns and North[5], only 1 of their patients was thought to have moyamoya-like vasculopathy. In these 4 published studies, about half of cerebral vasculopathy patients had moyamoya syndrome (23 patients among 47 cerebral vasculopathy patients)

It is intriguing that the majority of these moyamoya-like vasculopathy cases were unilateral. In the 23 patients with moyamoya-like vasculopathy in these 4 published studies, 19 patients had a unilateral abnormality. It is also noteworthy that only 8 of the 23 patients were symptomatic and 9 patients had clinical or radiological progressions during their follow-ups. The majority of asymptomatic patients in these studies were followed up with or without medication, such as aspirin. Surgery was usually reserved for the symptomatic and/or progressive patients.

The relatively low likelihood of symptomatic progression is contrasted with the high probability of pediatric moyamoya disease, in which about two thirds of patients experience symptomatic progression over time[41]. Routine MRI screening can help detect cerebral vasculopathy early in NF-1 patients before any related symptoms appear. In this regard, the proportions of bilateral and symptomatic patients were much higher (62% and 76%, respectively) in a surgical series of NF1-associated moyamoya syndrome patients, reflecting biases that were inherent in the observational and surgical patient cohorts[26].

Approximately 15% of NF-1 patients have an optic glioma. Cerebral vasculopathy is more frequently observed in patients with an optic glioma[12,39]. It was postulated that certain types of growth factors secreted from optic gliomas may contributed to vasculopathy development[39]. Furthermore, NF-1 patients have a threefold increased risk of developing moyamoya syndrome after irradiation for brain tumors, including optic gliomas, compared with non-NF-1 patients receiving the same treatment[48].

Neurofibromin, the product of NF1 gene is expressed in vascular endothelial cells and smooth muscle cells. NF1 is a tumor-suppressor gene that inhibits cell cycle progression[34]. The loss of NF1 can evoke inappropriate proliferation of vascular endothelial cells and smooth muscle cells leading to vascular wall thickening and stenosis. In an *in vitro* study, NF1 gene knockdown lead to increased proliferation of cultured human umbilical vein endothelial cell (HUVEC) and abnormal vascular morphogenesis[1]. Downstream targets of NF1, e.g., the RAS-RAF pathway and mTOR signaling cascade proteins, were activated in HUVECs. Furthermore, treatment of rapamycin, a mTOR inhibitor, restored the abnormal vascular network that was induced by NF1 knockdown. In a conditional NF1 knockout mouse model in smooth muscle cells, hyper-proliferative neointimal responses were observed after vascular injury[51]. Why the NF1-dependent signaling pathways disruption occurs in cerebral vessels and only in a minority of patients needs to be

further elucidated.

Routine brain MRI of NF1 patients is controversial. Some advocate brain MRI screening; however, others object to this because of the need for sedation in children, the high cost, and the low likelihood of intervention for frequently observed lesions[20]. Current guidelines for the NF-1 diagnoses and patient management do not advocate for routine neuroimaging applications for asymptomatic patients[50]. Considering the relatively low incidence of cerebral vasculopathy, especially for symptomatic cases, routine MRA screening is also not feasible. Careful clinical monitoring should be given to patients for possible TIAs, seizures, and neurological deficits development, and MRA should be reserved for symptomatic patients. Patients with optic gliomas and/or a history of cranial irradiation need special attention because they have higher risks of developing cerebral vasculopathy.

The surgical treatment for symptomatic NF1-associated moyamoya syndrome is similar to that of moyamoya disease. Encephaloduroarteriosynangiosis (EDAS), pial synangiosis, and direct bypass surgery have been applied to these patients[5,26]. However, there have only been a few large-scale studies dealing with surgical outcomes. A study from Boston Children's Hospital showed that 95% of 32 NF1-patients had a stable or improved neurological status long after pial synangiosis surgery[26]. Two patients had perioperative cerebral infarctions. However, during the follow-up periods, 5 patients developed new infarctions. Prior cranial irradiation was associated with new-onset infarctions after surgery.

DOWN SYNDROME

Moyamoya syndrome is observed in the Down syndrome population at a higher frequency than expected (Fig. 2). Although the association of these conditions has been recognized for a long time, it is a rare occurrence. There are scarce data regarding the incidence of concurrent moyamoya syndrome in Down syndrome patients. However, in a recently published study analyzing a nationwide admission database in the United States, the estimated Down syndrome prevalence was 3.8% in patients admitted with moyamoya disease[21]. The majority of patients were white and Hispanic, and 15% of the patients had ischemic strokes. This 3.8% concurrent prevalence may be an overestimate or limited to specific ethnic backgrounds, because Down syndrome is never represented in moyamoya disease populations to such a high degree in East Asian countries (personal communications).

The largest clinical series on Down syndrome with moyamoya syndrome included 16 surgically treated patients. All of these patients were symptomatic with focal neurological deficits and had bilateral involvement. The presenting symptoms were TIAs in 10 patients and infarctions in 6 patients; however, preoperative MRIs demonstrated that 15 patients had evidence of an infarction. Although this study contained only surgically treated patients, moyamoya syndrome associated with Down syndrome appears to be a clinically aggressive disorder. The surgical outcomes in this study were fair. Two patients had perioperative infarction and no patients experienced further infarctions during the follow-up period.

The pathogenetic mechanism of moyamoya syndrome that develops in Down syndrome patients is still obscure. Cardiac anomalies are found in 40−50% of Down syndrome patients, suggesting that the syndrome affects vascular system development in the whole body[49]. Markedly increased numbers of retinal vessels crossing the optic disc were observed in Down syndrome patients[2]. A low diabetic retinopathy prevalence, despite longstanding diabetes mellitus, and a markedly low solid cancer incidence were reported in Down syndrome patients[11,13]. Parsa and Almer[37] postulated that the reduced systemic angiogenesis and high endostatin levels observed in Down syndrome patients inhibited proliferative diabetic retinopathy and solid cancer growth, and promoted early branching of retinal vessels. This reduced angiogenesis capacity may be a link between Down syndrome and moyamoya disease.

Down syndrome is also associated with immunological abnormalities and these patients are prone to thyroid diseases and acute lymphocytic leukemia (ALL)[38]. In the surgical series previously mentioned, 1 patient had Hashimoto's thyroiditis and

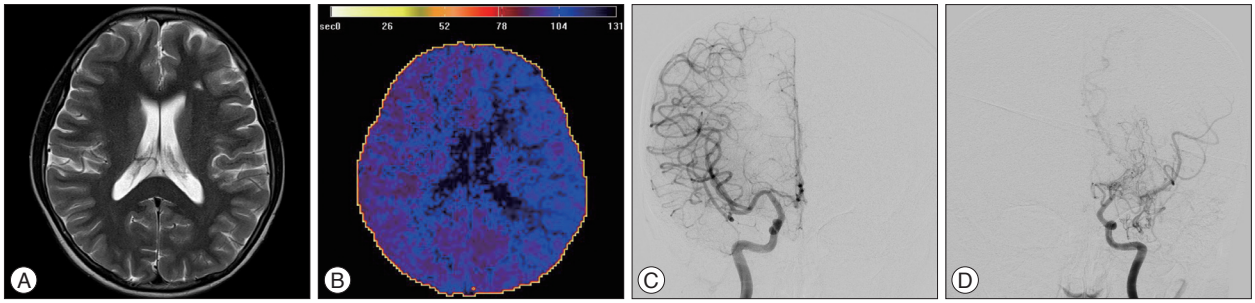

Fig. 2. A 9-year-old girl with Down syndrome had recurrent vomiting for 2 years. Examination of gastrointestinal system revealed no causes of the vomiting. A : A brain magnetic resonance image (MRI) was taken and an old small infarction was found in the left anterior watershed zone. The left middle cerebral artery trunk was invisible (not shown). B : A delayed time-to-peak in the left middle cerebral artery territory was observed in perfusion MRI. C and D : A subsequent angiography revealed a normal-looking right internal carotid artery and a near occlusion of left distal internal carotid artery with minute collateral vessel formation. Moyamoya syndrome was diagnosed. Although it was unclear that her vomiting was related to the cerebral vasculopathy, a pre-existing infarction warranted a surgical intervention. Encephaloduroarteriosynangiosis was performed on the left side. After surgery, her vomiting frequency decreased significantly. This patient illustrates the difficulty in evaluating neurological symptoms in Down syndrome patients.

type 2 diabetes mellitus, and 2 patients had Graves' disease. Another patient in the study had ALL and received cranial irradiation.[18] It is well known that moyamoya disease patients occasionally have thyroid dysfunctions[35]. The coexistence of moyamoya disease, Graves' disease, and type 2 diabetes mellitus was reported in Japanese patients[46]. Although the precise mechanism is still unknown, there is accumulating evidence that immunological triggering occurs in moyamoya disease. The immune dysregulation in Down syndrome may contribute to moyamoya syndrome development in some of the patients[29].

THYROID DISEASE

As stated in the Down syndrome section, thyroid dysfunction has been strongly associated with moyamoya syndrome. Ohba et al.[35] reviewed the reports of 31 patients with concurrent Graves' disease and intracranial arterial steno-occlusive disease published in the literature. There was a female predominance (28 women vs. 3 men) and the mean age was 29.3 years (range 10 to 54 years). All of the patients presented with an infarction and/or TIAs and there was no hemorrhagic presentation, which was not consistent with the usual presentation pattern of adult moyamoya disease. All of these patients, except 2 patients, were in a thyrotoxic state when the ischemic event occurred.

High levels of thyroid hormone can induce pathological vascular changes by altering the sensitivity to sympathetic stimuli[35]. In untreated Graves' disease patients, increased stiffness of the common carotid arteries was observed with untrasonography[7]. Hyperactivated hemodynamic states in thyrotoxicosis also contributes to cerebral infarction development when the vascular reserve is diminished by longstanding pathological changes[15].

Another hypothesis regarding moyamoya syndrome pathogenesis in Graves' disease entails the role of the immune system. Graves' disease is caused by the presence of serum autoantibodies to thyroid-stimulating hormone receptors[10]. An interesting study reported that moyamoya disease patients had significantly elevated levels of thyroid autoantibodies than non-moyamoya stroke patients and healthy controls, although all of the patients and controls were in a euthyroid state[24]. Therefore, autoimmune mechanisms may play a role in the pathogenesis, beyond the hemodynamic and sympathetic augmentation by excessive thyroid hormone. Moyamoya disease is also associated with other autoimmune diseases, such as antiphospholipid antibody syndrome, systemic lupus erythematosus, and ulcerative colitis, which further supports the autoimmune hypothesis[3,19,43].

The optimal treatment of Graves' disease-associated moyamoya syndrome is unclear as of yet. In a review by Ohba et al.[35] 16 patients received only medical anti-thyroid therapy and 11 patients received revascularization surgery. The treatment outcome was generally good and there was no apparent difference in the outcomes between the medical and surgical therapies. Appropriate anti-thyroid therapy can restore normal hemodynamic stress to the brain and lower the risks of ischemic attacks and infarction. However, revascularization surgery can reinforce brain perfusion when the vascular reserve is severely reduced by anatomical changes in the vessels. Im et al.[15] emphasized that revascularization surgery was warranted when a hampered cerebral vascular reserve was documented with single photon emission computed tomography because the future infarction risk was high in the event of a thyrotoxicosis relapse. To prevent perioperative infarction, keeping the patient in a strict euthyroid state before and after surgery is of paramount importance[15].

CRANIAL IRRADIATION

Although radiation induces damage to small-sized vasculature early, the endothelium of medium to large-sized vessels is also affected by the radiation in a delayed fashion[33]. Concomitant disruption of the microcirculation that supplies large vessels can exacerbate the damage. Intimal fibrosis and foamy cell accumulation ensues with resultant vascular stenosis and occlusion[6,9]. As a result of these pathophysiological changes in the cerebral vasculature, according to the Childhood Cancer Survivor Study, the relative risk for stroke is 37.2 for brain tumor survivors previously treated with radiation[4]. The cumulative stroke incidence at 25 years from the initial diagnosis was 6.9%[4]. Many of the cancer survivors suffering from stroke have a steno-occlusive disease reminiscent of moyamoya disease[33]. The incidence of this phenomenon is unclear, but a study reported that in 345 pediatric patients who were treated with radiation for various brain tumors, vascular abnormalities developed in 33 patients (9.6%) and 12 (3.5%) of them had vasculopathy compatible with moyamoya syndrome[48].

The risk of developing moyamoya syndrome is highest for patients who are irradiated for tumors typically located around the circle of Willis where the moyamoya pathognomonic vascular changes occur, such as optic glioma, craniopharyngioma, and germ cell tumors[23]. Optic glioma is of particular interest. According to the study mentioned above, in the 12 moyamoya syndrome patients, 10 patients received radiation for an optic glioma[48]. Many optic gliomas develop on the NF-1 background. NF-1 is an independent risk factor for moyamoya syndrome[33]. Therefore, there is an additive or even synergistic risk for moyamoya vasculopathy if these factors, which include NF-1, optic glioma, and irradiation, are combined in the same patient. There seems to present a dose-response relationship between radiation and moyamoya syndrome with increasing risks with escalating radiation dosage, especially over 50 Gy[48]. It is noteworthy that NF-1 patients are vulnerable to lower dose radiation. In a study of 54 patients with radiation-induced moyamoya syndrome, the average radiation dose was 46.5 Gy for NF-1 patients and 58.1 Gy for patients without NF-1[8]. Radiation-induced moyamoya syndrome occurs predominantly in children. Studies suggested that younger age at the time of irradiation increased the risk of moyamoya syndrome[8,33]. The time interval between irradiation and moyamoya symptoms onset is 2−5 years,

but it is highly variable[33,48].

The majority of patients with radiation-induced moyamoya syndrome are symptomatic[48]. Historically, they were mostly treated with revascularization surgery[28]. However, there is no consensus regarding the optimal management, largely because of the rarity of this condition.

CONCLUSIONS

Exploration of moyamoya syndrome can provide us with a different insight into moyamoya disease pathogenesis. It also confers a clinically valuable guide to manage the tricky diseases associated with moyamoya syndrome. And more importantly, many of the associated conditions were often weirdly interrelated. The interrelationship of NF-1, optic glioma, and irradiation is one example, and the immunological hypothesis binding Down syndrome, Graves' disease, and moyamoya disease together is another. More comprehensive epidemiological, genetic, and clinical studies will reveal the unknown facts and hidden links connecting all moyamoya-like vascular phenomena in the future.

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