Moyamoya syndrome after proton beam therapy in a pediatric patient with a pineal germ cell tumor and a germline polymorphism in *RNF213*

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22 **Abstract**

The effects of *RNF213*, which leads to moyamoya disease susceptibility, on radiation-induced moyamoya syndrome (MMS) remain unknown. We report a case of MMS after proton beam therapy (PBT) was deployed to treat a brain tumor in a patient with an *RNF213* polymorphism. An eight-year-old boy underwent whole ventricular and local PBT for a pineal germ cell tumor and was diagnosed with radiation-induced MMS nine months later. He underwent right and left revascularization surgeries for cerebral hemodynamic compromise at 17- and 18-years of age, respectively. Genetic analysis revealed a heterozygous germline polymorphism *RNF213* p.R4810K. This is the first report to suggest an association between *RNF213* polymorphism and radiation-induced MMS.

Keywords: moyamoya, proton beam, radiation, RNF213

23

Introduction

Moyamoya disease (MMD) is a progressive cerebrovascular disorder characterized by bilateral stenosis and occlusion of the distal carotid and proximal middle and anterior cerebral arteries [1]. Compared with conventional photon beam therapy, proton beam therapy (PBT) may reduce the risk of chronic adverse effects, such as secondary malignancies and neurocognitive dysfunction [2]. Despite the physical properties of proton beams, moyamoya syndrome (MMS) after PBT has recently been reported [3-12]. MMS, also called quasi-MMD, is excluded from primary MMD and defined as cerebrovascular lesions similar to MMD that are associated with other comorbidities, including autoimmune diseases, Down syndrome, neurofibromatosis type 1, and cerebrovascular lesions after head irradiation [13]. However, the genetic background of radiation-induced MMS and the association between *RNF213* [14, 15] and radiation-induced MMS remains uncertain. Here, we present a case of MMS after PBT for a pineal tumor in a patient with an *RNF213* polymorphism.

Case presentation

An eight-year-old boy was diagnosed with a pineal germ cell tumor after a biopsy. He received chemotherapy and whole ventricular and local PBT of 27.6 and 41.4 GyE, respectively (Fig. 1a-c). However, nine months later, magnetic resonance angiography revealed a de novo stenosis in the circle of Willis arteries. Cerebral angiography confirmed bilateral stenosis of the terminal internal carotid artery (ICA), M1, A1, and P1-2 portion of the major arteries (Fig. 1d). The patient was diagnosed with radiation-induced MMS, and aspirin was initiated. However, at the age of 17 years, he experienced repeated episodes of transient left-sided hemiparesis. Despite a signal decrease in the circle of Willis (Fig. 2a), the outer diameter of the affected arteries did not decrease on heavy T2 weighted imaging (Fig. 2b) and vessel wall imaging showed circumferential enhancement of the right terminal ICA

and M1 portion, which suggests radiation-induced MMS [13, 16, 17]. Single-photon emission computed tomography revealed bilateral cerebral hemodynamic compromise (Fig. 2d); consequently, he underwent direct and indirect combined revascularization surgery on the symptomatic right hemisphere [18] (Fig. 2e, f). Furthermore, when he was 18-years-old, he presented with an ischemic stroke in the left frontal lobe and progression of terminal ICA-M1 stenosis (Fig. 3a, b). He underwent direct and indirect combined revascularization surgery on the left side (Fig. 3c), with uneventful postoperative courses. We did not notice any differences in the intraoperative conditions of donor and recipient arteries compared with primary MMD. Hemodynamic compromise improved (Fig. 3d, e), and the transient ischemic attacks disappeared after revascularization surgery. The pineal tumor remained in remission for 10 years after PBT (Fig. 3f). Genetic analysis was conducted using peripheral blood as described previously [19], which revealed an RNF213 p.R4810K germline heterozygous polymorphism.

Discussion

Reports on MMS after PBT have recently emerged despite the expected safety of PBT compared with conventional photon therapy [3-12]. The reported incidence of cerebral vasculopathy after PBT ranges from 1% to 10%, and the latency period after PBT is 1–2 years. Hall et al. have reported the largest series of post-PBT vasculopathy, in which the incidence of severe vasculopathy requiring revascularization surgery was 0.6% (4/644) [7]. Whereas in our institute, all 30 children diagnosed with germ cell tumors since 2016 underwent PBT; thus, at our institute, the incidence of MMS after PBT was 3.3% (1/30) between 2016 and 2024. Regarding comparisons with photon therapy, Bavle et al. reported that after PBT, the incidence of radiation-induced vasculopathy was higher (6.2% vs 3%) and the latency period was shorter (1.4 - 2.3 years vs 2 - 28 years) [5]. These data suggest that the

radiation dose on the vasculature proximal to the target tumor can be higher in PBT than in photon therapy. Therefore, careful follow up and early detection of radiation-induced vascular abnormality is essential after PBT to prevent cerebral ischemia and to increase the efficacy of cerebral revascularization surgery [3, 7, 8, 11, 12, 20].

This is the first report on an association between *RNF213* and radiation-induced MMS. *RNF213* p.R4810K single-nucleotide polymorphism is a MMD risk factor in East Asian populations [14]. RNF213 is associated with endothelial function and vascular stability [21, 22], and *RNF213* p.R4810K is found in 2-3% of the normal population in East Asia [14]; thus, most carriers do not develop MMD. Reportedly, genetic manipulation of *RNF213* does not result in MMD in cells or animals [22, 23]. Therefore, a two-hit theory has been proposed, although the second factor remains unknown [24, 25].

Angiographic similarities between radiation-induced and primary MMD have been reported, including progressive occlusive disease, abnormal fine vessels, and transdural anastomosis [26][26]. One of the characteristic vascular histopathological findings in primary MMD includes intima fibrocellular thickening [27]. Radiation-induced vasculopathy also causes endothelial damage, with chronic endothelial proliferation that leads to progressive arterial stenosis [28, 29]. Contrastingly, recent MR vascular wall imaging studies may help differentiate radiation-induced arteritis from primary MMD, as described in the present case [13, 16, 17].

The causal relationship between the germline *RNF213* p.R4810K and the development of radiation-induced MMS remains undetermined in this report. However, the incidence of MMS after PBT in our institute (3.3%) was similar to that of *RNF213* p.R4810K carriers in the Japanese healthy population. Yet, it was higher than that of severe vasculopathy requiring revascularization surgery in Hall's study on a non-East Asian population. These data suggest the association between *RNF213* p.R4810K and radiation-

induced MMS, although *RNF213* genotyping was not performed in the rest of 29 children at our institute and it is the limitation. Furthermore, the short latency period and severe form of bilateral vasculopathy in the present patient also support this idea. However, further cohort studies are warranted to investigate the incidence of radiation-induced MMS in patients with *RNF213* p.R4810K and to elucidate the ethnic differences of radiation-induced MMS. Nevertheless, the present report suggests that *RNF213* p.R4810K could be a precipitating factor of radiation-induced MMS, and it may facilitate future studies.

Conclusion

This report presents MMS after PBT in a patient with the *RNF213* p.R4810K polymorphism, which is a potential risk factor for radiation-induced vasculopathy; however, the role of this gene on radiation-induced vasculopathy requires further investigation.

Figure Legends

Fig. 1 (a) Magnetic resonance image that shows a gadolinium-enhanced pineal germ cell tumor. (b) Magnetic resonance angiography shows no stenosis of major cerebral artery before proton beam therapy (PBT). (c) Dose distribution map of the PBT for whole ventricle and pineal tumor. (d) Cerebral angiography nine months after PBT shows bilateral stenosis of terminal internal carotid artery, M1, A1, and P1 portion of the arteries.

Fig. 2 (a) Magnetic resonance angiography (MRA) before the patient underwent right revascularization surgery. (b) Heavy T2-weighted images show that shrinkage of outer diameter does not occur in terminal internal carotid artery (ICA) and M1 portions (arrows). (c) Coronal and sagittal vessel wall imaging showed circumferential enhancement of right

terminal ICA and M1 portion (arrows). (d) Preoperative single photon emission computed tomography (SPECT) shows reduction of cerebrovascular reserve in the bilateral cerebral hemispheres. (e) Intraoperative view after completion of STA (asterisk)-middle cerebral artery anastomosis on the right side. (f) Postoperative MRA shows good patency of right direct bypass (arrowhead).

Fig. 3 (a, b) Magnetic resonance angiography (MRA) and diffusion-weighted imaging show progression of left terminal ICA-M1 portion stenosis (arrow) and infarction in the left frontal lobe, respectively. (c) Intraoperative view after completion of STA (asterisk)-middle cerebral artery anastomosis on the left side. (d) Postoperative MRA shows good patency of left direct bypass (arrowhead). (e) Postoperative SPECT at rest shows improvement of cerebral blood flow in the bilateral frontal lobes. (f) Gadolinium-enhanced T1-weighted imaging 10 years after proton beam therapy confirms the remission of the pineal germ cell tumor.

Compliance with ethical standards

Ethics approval: This study was approved by the Institutional Review Board of the Hokkaido University Hospital (approval number 14-053).

Conflict of interest: The authors have no relevant financial or non-financial interests to disclose.

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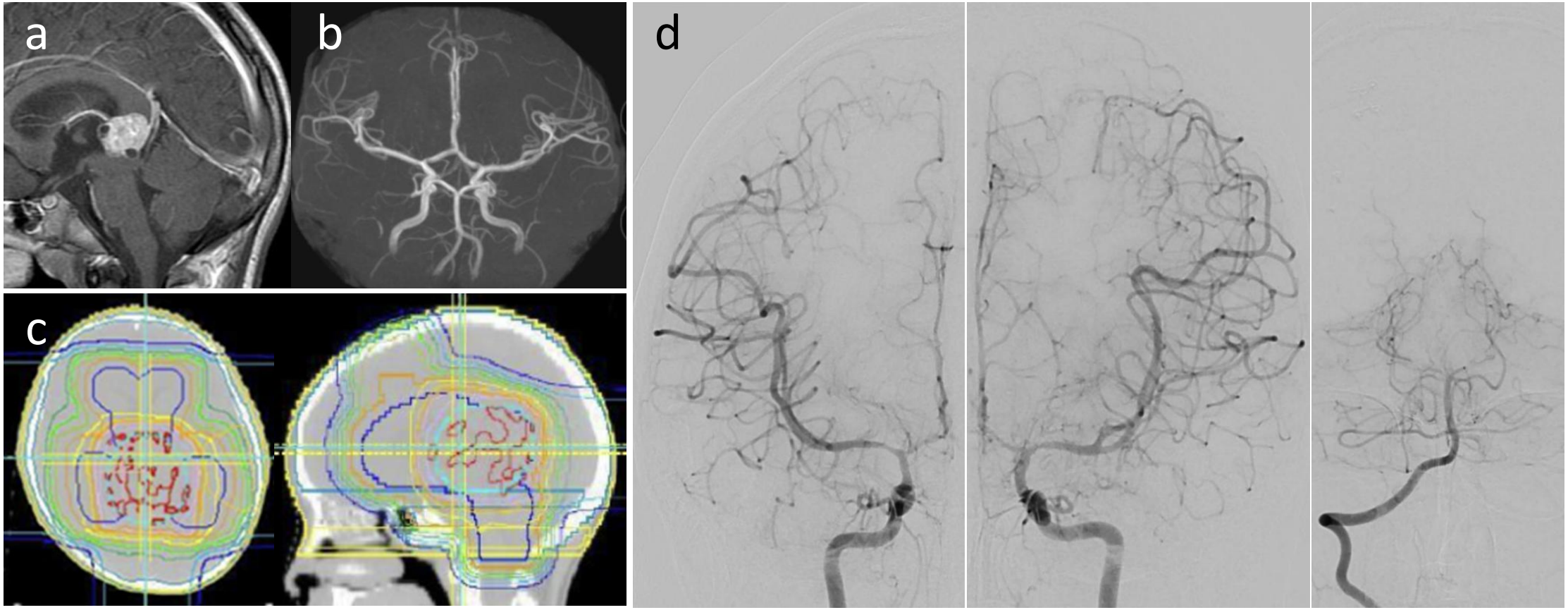
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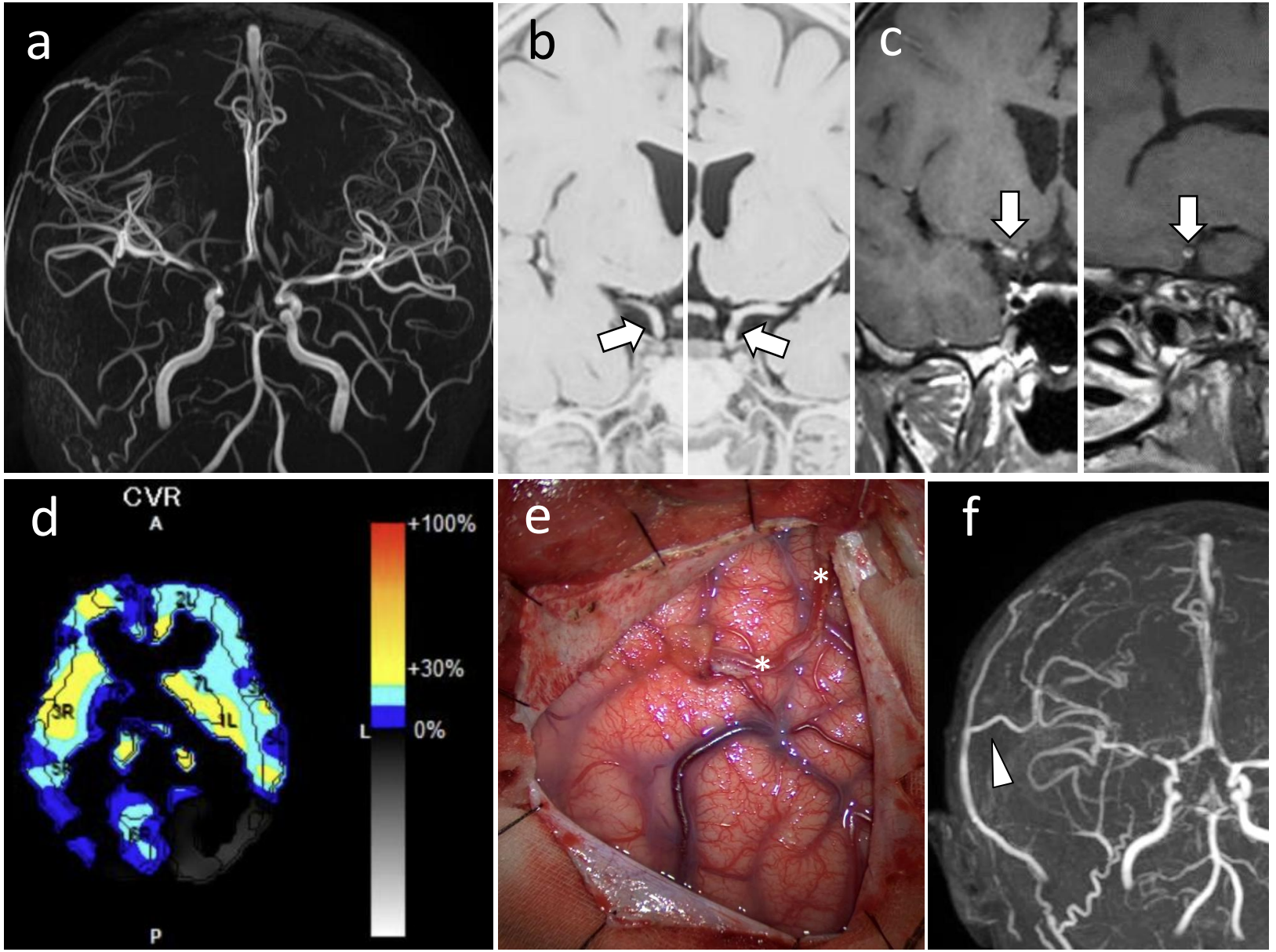
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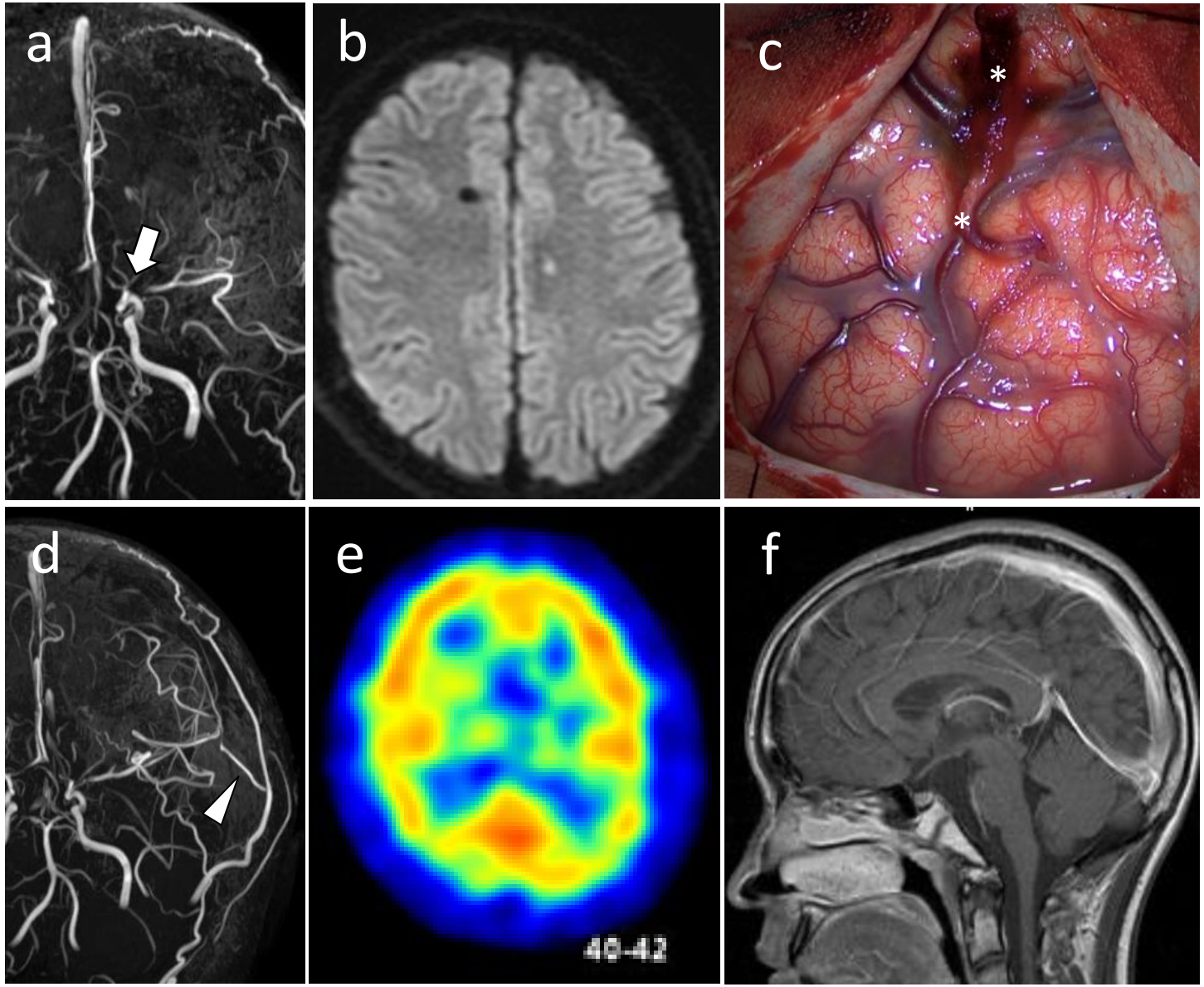
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