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Hereditary Hemorrhagic Telangiectasia: Recognizing, Screening and Treating from a Neurological Point of View

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Abstract: ***The Osler-Weber-Rendu condition, also known as hereditary hemorrhagic telangiectasia (HHT), is a rare genetic disorder affecting various areas of the human body. Two prevalent genotypes involve mutations in the endoglin gene (HHT-type 1) and the ALK-1 gene (HHT-type 2). These genetic alterations result in abnormal blood vessels, such as arteriovenous malformations (AVMs) in the liver, lungs, and brain (1) . Patients frequently experience continuous nosebleeds and gastrointestinal bleeding, leading to iron deficiency anemia. Liver and lung AVMs can lead to various clinical presentations, including portal hypertension, encephalopathy, and high-output cardiac failure in the liver, and shortness of breath, respiratory distress, and stroke events in the lungs (2). The prevalence of brain AVMs in HHT patients ranges from 10-20% (3, 4) , more frequently linked to the HHT-type 1 genotype. Symptoms include headaches, seizures, and intracranial hemorrhage (ICH). Identifying affected patients can aid in family-wide screening, resulting in improved diagnostics and patient outcomes. Neurointerventionalists play a crucial role in diagnosing and treating cerebral vascular malformations, with most of the brain AVMs being categorized as Spetzler-Martin grades I-II (5) . A comprehensive physical examination, can lead to the observation of several HHT symptoms in such patients, leading to an Osler-Weber-Rendu disease clinical diagnosis. All patients should undergo diagnostic MRI or CT scans, which would verify the presence of a brain AVMs, and subsequently be discussed for endovascular therapy.***

Keywords: Hereditary hemorrhagic telangiectasia, embolization

1. Illustrative Case

A 42-year-old female experienced a sudden onset of symptoms in October 2021, including a severe headache, right-sided weakness, and mixed aphasia. A head CT scan disclosed a left hemisphere hematoma, which was surgically evacuated. A subsequent MRI identified an arteriovenous malformation (AVM) as the hemorrhage's cause. She was admitted to our hospital in November to undergo AVM embolization to prevent future complications. A physical examination revealed mucocutaneous telangiectasia in various body areas (Figure 1.). We made a decision to treat the AVM to avoid recurrent hemorrhagic complications. A digitally subtracted angiography (DSA) revealed a small Spetzler-Martin Grade 2 AVM in the patient's left fronto-parietal region (Figure 2. A, B). Using a 5cm Apollo microcatheter, the main feeding vessel of the malformation, originating from the left middle cerebral artery (MCA), was selectively navigated (Figure 2. C, D). The AVM was embolized using EVOH (Ethylene Vinyl Alcohol Copolymer-Menox) (Figure 3.) with a satisfactory intra-procedural DSA result (Figure 3. C., D.). The patient was discharged three days later without any new neurological deficits. A follow-up MRI two months later showed no residual AVM and observed post-operative and post-hemorrhagic changes (Figure 4.).

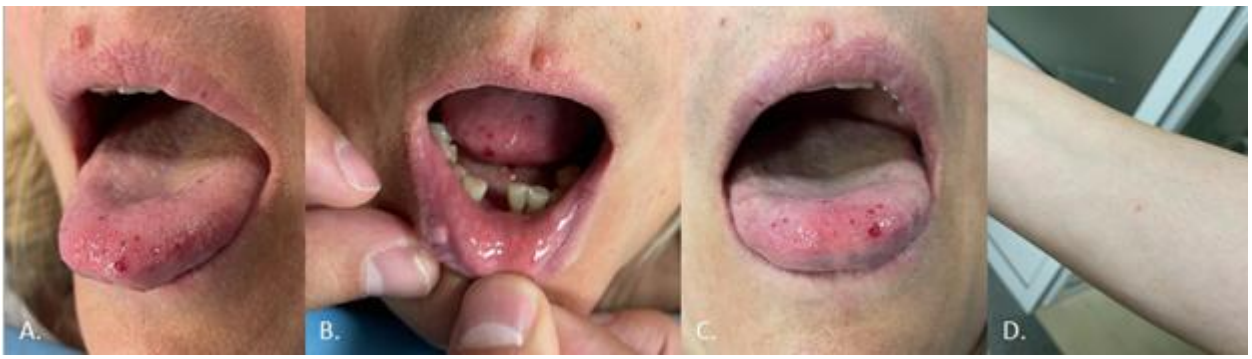

Figure 1: A, B, C, D: Our own archive of photos of physical findings on the patient. Upon physical examination we found multiple mucocutaneusteleangiectasias, most notably on the tip of the tongue.

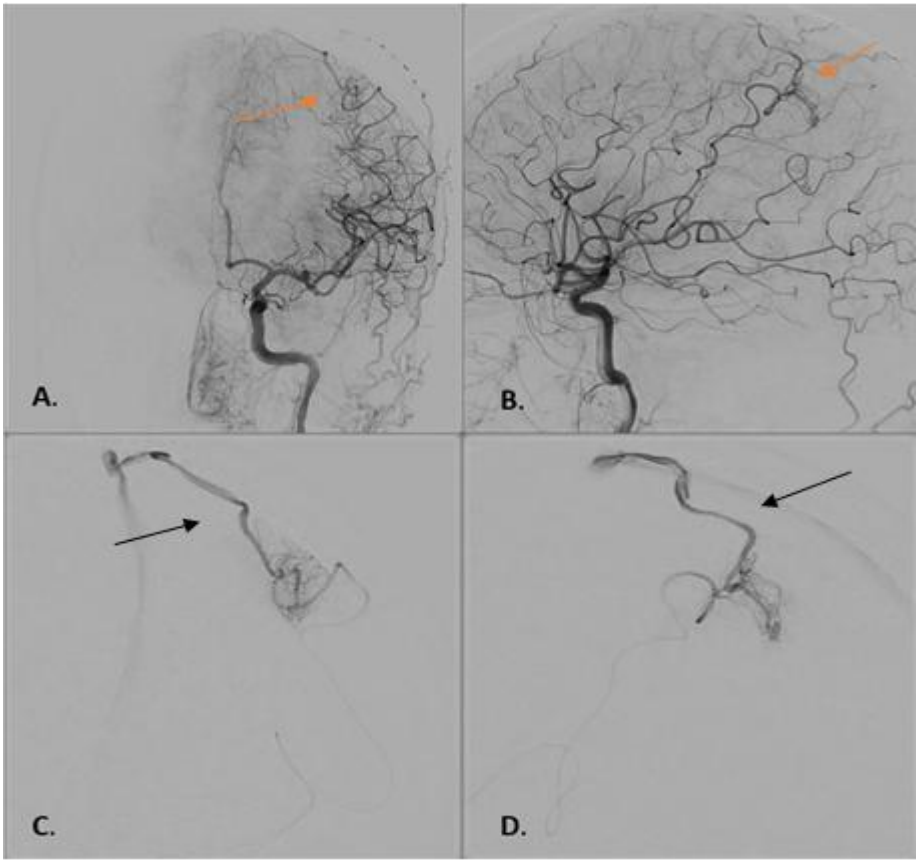

Figure 2: A, B, C, D-Intraprocedural DSA of the left Internal carotid artery (A, B), and the feeding vessel of the AVM nidus (C, D). A (Antero-posterior projection) and B (Lateral projection) show a small AVM nidus (orange arrows) with feeding arteries arising from distal branches of the left Middle cerebral artery. Selective catheterization of such a branch visualized the nidus with a dilated cortical vein (black arrows) draining the nidus into the Superior sagittal sinus.

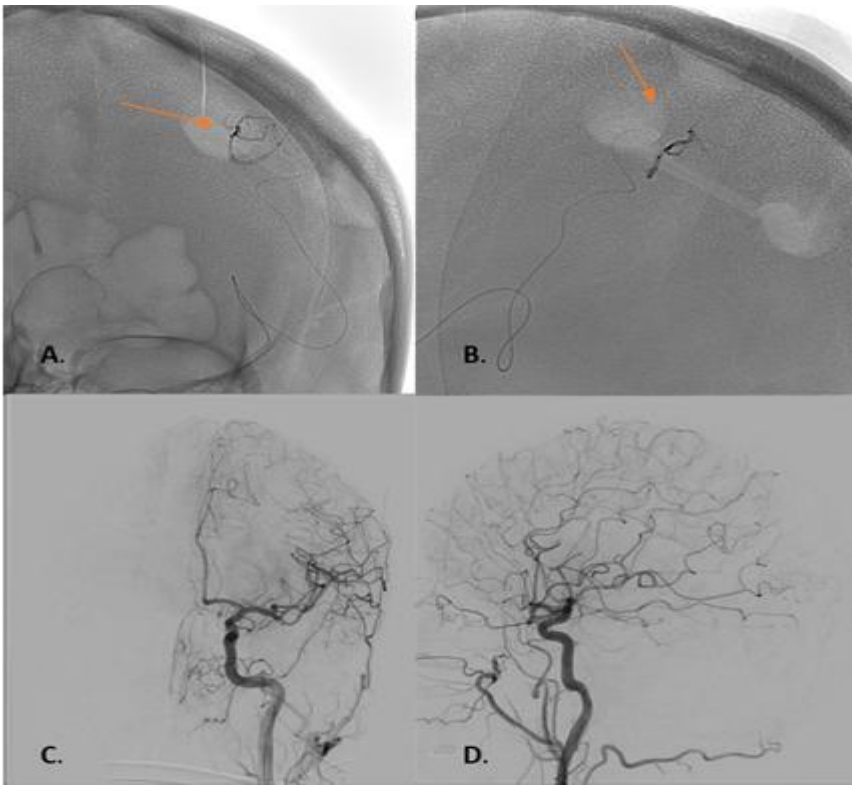

Figure 3: A (AP projection), B (Lateral projection): Single shot images of the Menox cast (orange arrows) of the embolized AVM, with a still undetached microcatheter. C, D: AP and lateral view of the post-procedural DSA showed complete occlusion of the AVM and disappearance of the draining vein.

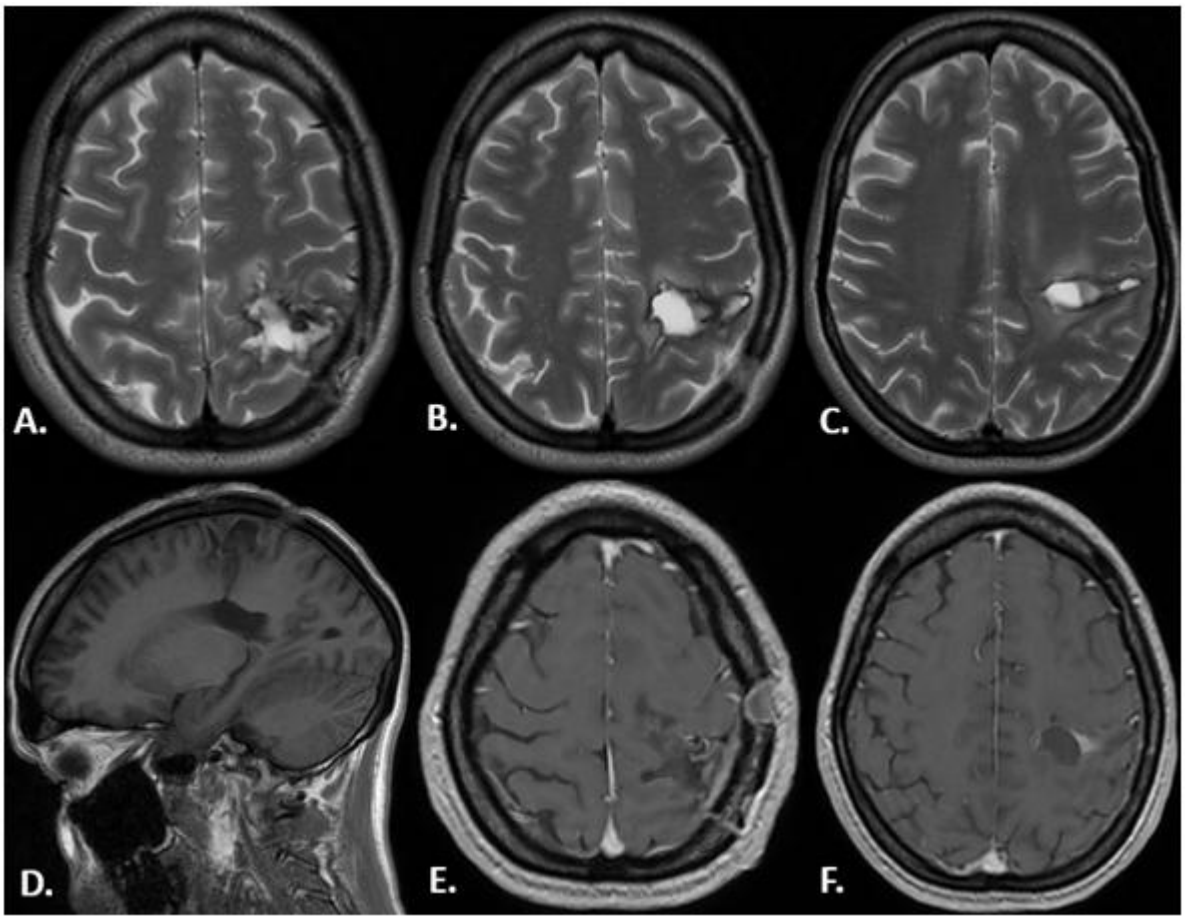

Figure 4: A, B, C: Axial T2-weighted images. D: Sagittal T1-weighted image. E, F: Axial T1-weighted images with contrast enhancement. The 3-mmonth follow up MRI showed no residual AVM nidus being present. Post-operative and post-hemorrhagic changes at the site of the previously bled and embolized AVM can be observed.

2. Discussion

Since first being described by physicians, the knowledge acquired on the syndrome throughout history has greatly improved (6) . Genetic analysis led to the discovery of several main genes that are responsible for the formation of the vascular malformations throughout the body with subsequent symptoms being present. The diagnosis is formally based on the Curaçao criteria (7) .

As neurointerventionalists, we turn our main focus towards the nervous system presentation of the disease. As it was established, the majority of brain AVMs that are observed in such patients are a low-grade and accessible for both surgical resection and endovascular embolization. Often times due to the presence of multiple AVMs, the surgical approach has a downfall, relating to its more invasive nature and possibly difficult to reach deep-seated locations. We emphasize on the need for a multidisciplinary approach to treating these vascular pathologies, especially in the setting of HHT (8) , as not one method has a definitive advantage over the rest, when it comes to curing the pathology (9) . When a patient present with HHT, a question of screening for the disease also arises. As it is autosomal-dominant in nature, we can expect relatives of the patient to have a risk of carrying gene mutations related to the disease. Some studies show a hemorrhagic rate of HHT AVMs over 20%, which is in no way a negligible risk (10) . There was a statistical correlation showing that different genotypes relate with different phenotypes of the disease, which would correlate with an increased risk of intracranial hemorrhage.

Screening of these patients is a controversial topic, with the general consensus being against, rather than for screening (11) . Newer data shows that even after a negative imaging acquisition for AVMs, de novo formation is not excluded throughout the lifespan of the individual, as the vascular malformation in itself is a dynamic entity, with remodeling happening in the angioarchitecture constantly (12) . Factors, such as malformation phenotype, size and location of the AVM may steer the decision on whether or not it should be treated or regarded as a no-touch lesion (13, 14) .

There is a difference in guidelines between the North American centers and European ones on whether or not screening should be performed, with the former ones doing it routinely, which further goes to show the lack of a unanimous stand on the matter. One point against searching for the cerebral manifestation is often the lack of clinical presentation of the AVMs, until their rupture. Furthermore, we cannot rely on larger studies such as the ARUBA trial (15) , as it did not specify the inclusion of HHT patients in its cohorts. Having these discrepancies between different schools of medicine and with a not at all unified opinion on the matter, the decision on whether or not a patient should be screened, treated and which method of treatment would be most adequate is often left purely on the multidisciplinary team of physicians that are involved in each case.

Characteristics of the AVM, age of the patient, history of intracranial hemorrhage and presence of symptoms should be taken into account and the decision should be made on a case-by-case basis.

3. Conclusion

Patients with specific symptoms of HHT can and should be screened for the presence of brain AVMs, with de novo formation in adulthood being a possibility. The treatment modalities chosen must be best suited for each individual case, with the risk of rupture being non-negligible. In cases of HHT, endovascular embolization of brain AVMs is a safe and effective treatment option, which can act as a stand-alone treatment modality.

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