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The potential of capillary birthmarks as a significant marker for capillary malformation–arteriovenous malformation syndrome in children who had nontraumatic cerebral hemorrhage

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Abstract

Background/Purpose: Capillary malformation–arteriovenous malformation (CM-AVM) is a new autosomal dominant disorder with cutaneous capillary malformations (CM) and high-flow cerebral arteriovenous malformations (AVM). Patients may have Parkes-Weber syndrome. This study determined if cutaneous CM are a significant indicator of CM-AVM in children with cerebral bleeds.

Methods: Children with cerebral AVMs between 1991 and 2009 were reviewed. A family history of brain hemorrhage, AVMs, or cutaneous birthmarks was elicited. Patients and siblings were examined for CM and a family tree recorded. A brief questionnaire determined the family's opinion regarding screening for this syndrome.

Results: Of 30 families, 1 family had Parkes-Weber syndrome. In 3 families, both patient and relatives had CM. In 9 families, patients had no CM, but relatives had them. One family had hereditary hemorrhagic telangiectasia. From the survey, 80% of families would be concerned about vascular marks, and 87% of families would allow screening for cerebral AVMs.

Conclusion: A family history of vascular marks may predict families at risk of having a cerebral AVM with hemorrhage. Most families would agree to screening. However, family history and physical examination alone do not confirm CM-AVM but form a useful screening tool to identify families needing further investigations with genetic testing and/or magnetic resonance imaging.

Vascular anomalies are localized structural defects in the vasculature caused by abnormal morphogenesis during development [1]. Cutaneous lesions such as port-wine stains are common and present in 0.3% to 0.5% of the population, and are also present in some complex vascular syndromes,

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such as Klippel-Trenaunay syndrome, Sturge-Weber syndrome and Parkes-Weber syndrome (PWS) [2-4]. Arteriovenous malformations (AVM) are also common but are difficult to diagnose clinically and may be mistaken for capillary malformations or hemangiomas, unless investigated by ultrasonography and color Doppler examination [5-7].

Arteriovenous malformations can harm tissues by compromising oxygen delivery to adjacent tissues or by hemorrhage, as their walls are abnormal and weak. Mostly, these hemorrhages are microscopic, with limited damage, but in the brain they can lead to a major cerebrovascular accident or stroke [8]. Arteriovenous malformations account for about 1% of all strokes in adults, although in pediatrics they account for 10% to 15% of strokes [9].

Although AVMs have been regarded as sporadic lesions, it has been shown recently that AVM can be associated with capillary malformations (CM) on the skin, in a new autosomally dominant syndrome known as CM-AVM [10,11]. A gene encoding p120-RasGAP, called the *RASA1* gene, has been identified as mutated in CM-AVM patients [12,13]. The CM in this syndrome may be small and subtle and could easily be overlooked in a patient presenting with a cerebral hemorrhage [14].

In this study, we aimed to determine if children treated for cerebrovascular hemorrhage could be identified as being likely to have CM-AVM syndrome (caused by *RASA1* mutations) by the presence of CM on their skin. We hoped to establish the prevalence of CM-AVM in patients with cerebral hemorrhage, and determine their attitude to gene and morphological screening.

1. Methods

All patients admitted between January 1991 and September 2009 with a cerebral hemorrhage were identified from the hospital records. The records were examined on the electronic database to determine all those with a cerebral hemorrhage but with no other identifiable cause, such as tumors, trauma, hydrocephalus or prematurity.

Eligible patients were traced by address and phone number and invited to participate in the audit, as approved by the institutional ethics committee (CA29091). From patients who agreed to participate, background data were gathered from the medical records, and a physical examination of the patient was conducted to search for cutaneous CM. If any lesions were found, a detailed account was made and photographs taken and stored with the patient's record.

Family members were also examined after informed consent and a detailed family tree constructed. Each family was given a short questionnaire to assess the patients' attitudes to possible identification of a link between the cerebral AVM and an inherited syndrome, such as CM-AVM, that may have implications for other family members. Answers were scored 1, very unlikely; 2, unlikely; 3, no opinion; 4, likely; and 5, very likely. The 6 questions asked were as follows: (1) If a link between birthmarks on the skin

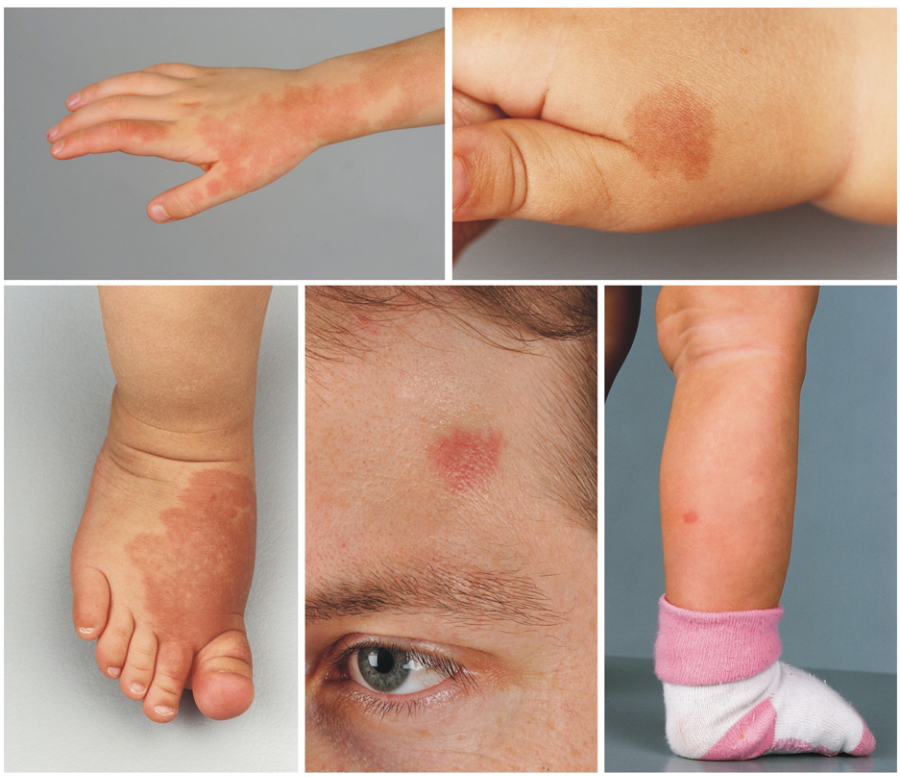

Fig. 1 Typical cutaneous CM, as seen in patients with CM-AVM syndrome, as shown to all families in the audit.