Research letter

Infantile haemangiomas do not occur more frequently in children with congenital melanocytic naevi

DOI: 10.1111/bjd.14791

Dear Editor, Infantile haemangioma (IH) is a very common benign vascular tumour with a reported incidence of 4–10% in infants,[1] and no clear genetic basis described as yet.[2] Congenital melanocytic naevi (CMN) are benign melanocytic tumours present in 1% of newborns, which when multiple are caused by post-zygotic mutations in the gene *NRAS* in the majority of cases,[3] and when single, carry various somatic mutations where causality is difficult to prove.[4–6] Melanocytic and vascular anomalies can coexist in the condition phakomatosis pigmentovascularis (PPV), and the same genetic mutation is responsible for both cutaneous lesions;[7] however, these do not involve either CMN or IH. Moreover, the vascular lesion in PPV is considered congenital and malformative as CMN, and not proliferative and acquired as IH.[8] A case series of six patients presenting with both CMN and IH has been reported previously, where the authors hypothesized that this co-occurrence might be more common than expected by chance.[9]

To test this hypothesis we conducted a systematic evaluation of the presence of IH in the cohort of patients with CMN seen in our tertiary referral service over a 10-year period between March 2006 and February 2016. All children were examined by the same physician, and data were collected prospectively. We included in this analysis only children less than 3 years of age at the examination date, as the natural history of IH is to spontaneously involute during the first few years of life.

A total of 244 patients with CMN under the age of 3 years were seen in this time period, with a mean and median age of 0·78 years and 0·53 years, respectively. Of these, 142 were females, giving the same male : female ratio of 1 : 1·4 as has previously been reported for our CMN cohort.[10] Fourteen patients were recorded as having an IH (5·7%), compatible with prevalence figures for the general population. Furthermore, the characteristics of those with an IH mirror those of the general population, as the male : female ratio for those with IH and CMN was 1 : 6. Table 1 shows the clinical characteristics of the patient cohort, comparing those with and without IH. The number of patients with CMN and IH is too small to perform a statistical comparison of the severity of CMN phenotype, but clinical phenotyping data are shown in Table 1.

This systematic study of the prevalence of IH in a cohort of patients with CMN has found no increase above that of the normal population, and a sex ratio in line with what we would expect for IH alone. This study does not support a connection at a genetic level between CMN and IH, either at germline predisposition or at somatic mutation level.

Table 1 Clinical characteristics of patients with congenital melanocytic naevi (CMN) with and without infantile haemangioma (IH)

	Patients with CMN, n (%)	Patients with CMN + IH, n (%)
Sex		
Female	130 (56·5)	12 (85·7)
Male	100 (43·5)	2 (14·3)
Total	230 (100)	14 (100)
Projected adult size		
< 10 cm	58 (25·2)	1 (7·1)
10–20 cm	45 (19·6)	3 (21·4)
20–40 cm	52 (22·6)	4 (28·6)
40–60 cm	25 (10·9)	3 (21·4)
> 60 cm	39 (17)	1 (7·1)
Multiple small or medium	7 (3)	2 (14·3)
Missing	4 (1·7)	0
Approximate total number of naevi at examination date		
1	34 (14·8)	0
2–9	55 (23·9)	2 (14·3)
10–19	33 (14·3)	2 (14·3)
20–50	33 (14·3)	0
50–100	25 (10·9)	0
100–200	17 (7·4)	2 (14·3)
> 200	4 (1·7)	1 (7·1)
Missing	29 (12·6)	7 (50)
Location of principal CMN		
Face	17 (7·4)	0
Scalp	21 (9·1)	1 (7·1)
Neck	1 (0·4)	0
Trunk	80 (34·8)	3 (21·4)
Limb	26 (11·3)	3 (21·4)
Scalp, neck and trunk	8 (3·5)	0
Face and scalp	16 (7·0)	0
Multiple	4 (1·7)	1 (7·1)
Missing	57 (24·8)	6 (42·9)
Location of haemangioma		
Face		1 (7·1)
Head and neck (nonfacial)		0
Trunk		6 (42·9)
Extremity		3 (21·4)
Missing		4 (28·6)

V. Martins da Silva[1,2]
V. Kinsler[1,3]

[1]*Genetics and Genomic Medicine, UCL Institute of Child Health, London, U.K.*
[2]*Department of Medicine, University of Barcelona, Barcelona, Spain*
[3]*Department of Paediatric Dermatology, Great Ormond Street Hospital for Children, London, U.K.*
Correspondence: Veronica Kinsler.
E-mail: v.kinsler@ucl.ac.uk

References

1 Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. *Pediatr Dermatol* 2008; **25**:168–73.
2 Fernando Greco M, Frieden IJ, Drolet BA *et al.* The Hemangioma Investigator Group. Infantile hemangiomas in twins: a prospective cohort study. *Pediatr Dermatol* 2016; **33**: 178–83.
3 Kinsler VA, Thomas AC, Ishida M *et al.* Multiple congenital melanocytic nevi and neurocutaneous melanosis are caused by postzygotic mutations in codon 61 of NRAS. *J Invest Dermatol* 2013; **133**:2229–36.
4 Papp T, Pemsel H, Zimmermann R *et al.* Mutational analysis of the N-ras, p53, p16INK4a, CDK4, and MC1R genes in human congenital melanocytic naevi. *J Med Genet* 1999; **36**:610–14.
5 Papp T, Schipper H, Kumar K *et al.* Mutational analysis of the BRAF gene in human congenital and dysplastic melanocytic naevi. *Melanoma Res* 2005; **15**:401–7.
6 Bauer J, Curtin JA, Pinkel D, Bastian BC. Congenital melanocytic nevi frequently harbor NRAS mutations but no BRAF mutations. *J Invest Dermatol* 2007; **127**:179–82.
7 Thomas AC, Zeng Z, Rivière J-B *et al.* Mosaic activating mutations in *GNA11* and *GNAQ* are associated with phakomatosis pigmentovascularis and extensive dermal melanocytosis. *J Invest Dermatol* 2016; **136**:770–8.
8 Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg* 1982; **69**:412–22.
9 Wu PA, Mancini AJ, Marghoob AA, Frieden IJ. Simultaneous occurrence of infantile hemangioma and congenital melanocytic nevus: coincidence or real association? *J Am Acad Dermatol* 2008; **58** (Suppl. 2):S16–22.
10 Kinsler VA, Birley J, Atherton DJ. Great Ormond Street Hospital for Children Registry for Congenital Melanocytic Naevi: prospective study 1988–2007. Part 1: epidemiology, phenotype and outcomes. *Br J Dermatol* 2009; **160**:143–50.

Funding sources: this research was funded by the Wellcome Trust, award number WT104076MA, and supported by the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London, and by Caring Matters Now Charity and Patient Support Group. The funders had no role in the design and conduct of the study; in the collection, analysis and interpretation of the data; in the decision of the submission of the manuscript; or in the preparation, review or approval of the manuscript.

Conflicts of interest: none declared.