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Routine liver ultrasound screening does not alter clinical management in a cohort study of multiple cutaneous infantile haemangioma

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To the Editor,

Cutaneous infantile haemangioma (IH) occurs in 5-10% of neonates, with multiple IH (>1) in 30% of those[1]. Expert opinion currently recommends routine liver ultrasound(USS) for five or more(5^+) IH[2,3], and if hepatic haemangiomas(HH) are identified, to test thyroid function[3] even if neonatal thyroid screening occurred. Supportive data from one cohort demonstrate associations between 5^+ IH and HH[1], and between HH and adverse clinical outcomes (cardiac failure/hypothyroidism)[4-6]. However, there are no data relating number of cutaneous IH, USS screening, or thyroid testing to frequency of adverse clinical outcomes, as per the principles of any screening programme[7]. One study suggesting validation of screening USS in infants with multiple cutaneous IH, whilst important in describing a HH cohort, in fact compared clinical outcomes in infants presenting spontaneously (in whom we would expect more severe disease) with those diagnosed on screening[4]. In addition, it lacked control groups without USS and without HH.

Three fundamental questions therefore remain: 1) is there is a statistically-significant association between number of cutaneous IH and adverse clinical outcome? 2)does screening USS alter rates of adverse clinical outcome? and 3) does thyroid function re-testing of those with HH alter clinical outcome? Whilst this is a large study and every attempt has been made to collect and analyse data accurately, a prospective randomised control trial will be the only way to answer questions 2/3 definitively.

Two retrospective cohorts were identified from electronic patient records search, and combined: infants with multiple IH (seen 1996-2016), and solitary IH (2015-2016), to assess question one. As screening advice changed over twenty years, we were able to include infants with and without liver USS and repeat thyroid testing, to assess questions two and three. Infants with PHACE were excluded, and no patient had multifocal lymphangiomatosis with thrombocytopaenia[8]. Median age at presentation to our department with IH was 0.50y (mean 0.92, SEM 0.05), with 0.47y for the subset with multiple IH (mean 0.65/SEM 0.03), and 0.21y for those with cardiac failure (mean 0.33/SEM 0.08). Age at first USS in our hospital was median 0.39 (mean 0.56/SEM 0.04).

843 infants were studied, 74% female, 83% with multiple IH. There were no deaths. 19%(71/381) of those screened by USS had HH (10 single, 58 multiple, 2 diffuse and 1 multiple-almost-diffuse), of which more than a third (24/71) had <5 IH and would have been missed by current screening recommendations. Despite the high rate of HH, <1% (8/843) required treatment for cardiac failure and <1% (6/843) for hypothyroidism (one patient requiring treatment for both), in line with previous reports[3]. 6/13 requiring treatment had <5 IH, and 8/13 had HH.

Overall, the number of cutaneous IH was not significantly associated with treatment for cardiac failure or hypothyroidism on regression analysis with Bonferroni correction (p=0.038 and p=0.760 respectively) (**Figure 1a,b**). Grouping by IH number, two potentially interesting findings were: there were no cases of single IH with cardiac failure, and there was a significant difference in cardiac failure rate between those with 1-9 IH and those with 10 or more, but not between 1-4 and 5-9 (**Figure 1c**). The total number of cases with adverse clinical outcomes was however very small, and these attempts to answer question one may still be underpowered.

All eight cases treated for cardiac failure had cardiorespiratory symptoms/signs at first presentation to medical services with IH, and treatments were given on that basis rather than on USS result (1 normal, 1 portocaval shunt without HH, 2 solitary HH, 3 multiple, 1 diffuse). Furthermore, in 5/8 cases treatment was deemed or demonstrated to be due to a cardiovascular cause requiring surgical correction, rather than HH, potentially reflecting the confounding influence of prematurity on both structural cardiac defects and multiple IH.

3/6 cases treated for hypothyroidism were detected by neonatal screening (2 with normal USS, 1 diffuse HH), 2/6 had no Guthrie result available (1 multiple HH, 1 multiple-almost-diffuse), and one had normal Guthrie (normal USS). The incidence of congenital hypothyroidism in the UK is 0.6/1000[6], which is not significantly different from this study or previous reports[3]. Retesting of thyroid function in those with multiple HH would therefore have missed the only case definitely missed by Guthrie screening.

On the basis of these data, we suggest that all infants should have a thorough clinical assessment on presentation with any number of IH, and if there are concerns about cardiac failure or hypothyroidism should be referred that day to a specialist. If there are no concerns, parents should be made aware of the early symptoms and signs, such as lethargy and poor feeding, and have rapid access to a physician if these develop. In our practice, use of USS will now be based on signs/symptoms of cardiac failure, independent of cutaneous IH number. Our data do not support routine re-screening for hypothyroidism for those with HH, however numbers of cases are low. Going forwards, a very large prospective randomized control trial of infants with all numbers of cutaneous IH will be required to assess the validity of USS and/or repeat thyroid testing compared to clinical assessment.

Figure 1

Frequency of a) cardiac failure requiring treatment and b) hypothyroidism requiring treatment demonstrating cases with fewer than 5 IH in both groups who would not be detected by current recommendations for screening; c) percentage of cases of cardiac failure requiring treatment by grouped number of cutaneous IH, demonstrating lack of significance between 1-4 and 5-9 IH, but a significant difference between 1-9 and 10 or more p<001, two-way Fisher's exact test).

References

1 Haggstrom AN, Drolet BA, Baselga E *et al.* Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. *Pediatrics* 2006; **118**: 882-7.

2 Dickie B, Dasgupta R, Nair R *et al.* Spectrum of hepatic hemangiomas: management and outcome. *J Pediatr Surg* 2009; **44**: 125-33.

3 Horii KA, Drolet BA, Frieden IJ *et al.* Prospective study of the frequency of hepatic hemangiomas in infants with multiple cutaneous infantile hemangiomas. *Pediatric dermatology* 2011; **28**: 245-53.

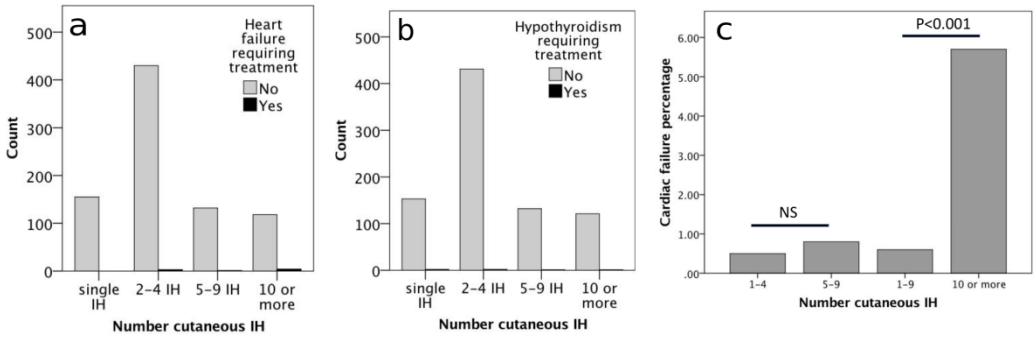
4 Rialon KL, Murillo R, Fevurly RD *et al.* Impact of Screening for Hepatic Hemangiomas in Patients with Multiple Cutaneous Infantile Hemangiomas. *Pediatric dermatology* 2015; **32**: 808-12.

5 Huang SA, Tu HM, Harney JW *et al.* Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. *The New England journal of medicine* 2000; **343**: 185-9.

6 Simsek E, Demiral M, Gundogdu E. Severe consumptive hypothyroidism caused by multiple infantile hepatic haemangiomas. *Journal of pediatric endocrinology & metabolism : JPEM* 2018; **31**: 823-7.

7 Wilson J, Jungner, G. . Principles and practice of screening for disease. . In: *Public Health Paper Number 34.* Geneva: World Health Organisation. 1968.

8 North PE, Kahn T, Cordisco MR *et al.* Multifocal lymphangioendotheliomatosis with thrombocytopenia: a newly recognized clinicopathological entity. *Archives of dermatology* 2004; **140**: 599-606.



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