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CLINICAL REPORT

Skin Patterns Associated with Upper Airway Infantile Haemangiomas: A Retrospective Multicentre Study

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The aim of this study was to define the skin patterns at high risk for upper airway infantile haemangioma. A retrospective multicentre French observational study was conducted between January 2006 and January 2015 and all confirmed airway haemangioma were included. Thirty-eight patients with airway haemangioma from 9 centres were included. Thirty-one patients had a cutaneous or mucosal haemangioma: 21 with a location considered at high risk for airway haemangioma (large segmental mandibular haemangioma), 4 with a very mild facial involvement (lower lip or S1 (frontotemporal segment according to Haggstrom and Frieden)) and 6 with either lesions of the neck or body, or association of both. We report here the largest cohort of airway haemangioma. A third of patients do not completely fit with the definition of the high-risk area of airway haemangioma. Segmental lower lip and neck involvement also seem to be very suggestive areas. Clinicians must be able to recognize these areas.
Key words: haemangioma; pattern; airway haemangioma.

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Infantile haemangiomas (IH) are common benign vascular tumours affecting 4–10% of children (1). Their natural course comprises a phase of proliferation over the first 9–12 months, followed by a spontaneous resolution. Therefore, treatment is not required in the majority of cases except for severe or complicated ones, for which propranolol is recently considered as the treatment of choice (2). Severe or complicated forms represent up to 24% of IH and comprise ulceration, soft-tissue deformity or airway obstruction due to upper airway haemangioma (UAIH) (3). The latter is a rare situation with an incidence that is not properly known. It may be life threatening, necessitating an early intervention before the occurrence of severe respiratory signs, such as biphasic stridor and severe respiratory distress. More than 50% of UAIH are associated with a cutaneous IH in a particular distribution (4). Orlow et al. (5) were the first authors to describe these particular skin patterns associated with a high risk of UAIH. In a large retrospective study of 529 patients including 182 patients with IH located on head and neck, he identified the beard distribution as a high-risk area. This distribution was defined by a scoring of 4 or above (1 point by affected area, 5 areas: left or right preauricular region, chin, lower lip and front part of the neck). Another retrospective study conducted by O et al. (6) included 1,226 patients with IH and used the term "mandibular area" (preauricular area, chin, lower lip, anterior portion of the neck) to describe this high-risk area for UAIH. Haggstrom et al. in a prospective study comprising 108 children with large facial IH demonstrated that patients presenting with segmental distribution of the facial area S3, often bilaterally, were at high risk of UAIH. The facial area was divided into 4 segments (S1–S4). Area S3 corresponds to the preauricular region, mandible, chin, and lower lip (lower cutaneous and vermillion) (Fig. 1) (7, 8). In our clinical practice, we observed that UAIH may be associated with more limited skin patterns. The aim of this study was to define the pattern of cutaneous IH associated with UAIH in a large cohort study.

MATERIALS AND METHODS

This was designed as a retrospective, multicentre, observational study. The study was in accordance with the principles of the Declaration of Helsinki 1975, revised 1983. It was approved by local ethics committee of Toulouse University Hospital and by the Commission National Informatique et Libertés (CNIL).

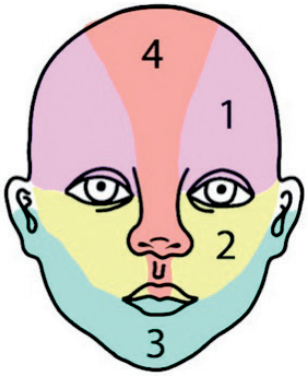

Fig. 1. Segmental repartition of facial infantile haemangioma according to Haggstrom and Frieden's classification (8).

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All the centres specialized in treating IH in France were contacted, including dermatologists, otolaryngologists and pneumologists. All patients with UAIH, seen between January 2006 and January 2015, were included. The skin pattern at high-risk for UAIH was defined as large segmental mandibular IH. The facial location of the cutaneous IH was described according to Haggstrom and Frieden's classification (8). UAIH were defined as an IH located in the upper airway, including subglottic, but also pharyngeal location. The diagnosis was based on clinical symptoms (respiratory signs and/or skin lesions) and confirmed by nasofibroscopy and/or magnetic resonance imaging. Data were collected from patient's medical records and photographs. A standardized questionnaire was completed, comprising the number of IH seen per year and patient's and IH's characteristics (date of birth, birth weight, medical history, description of the cutaneous IH if present, age at diagnosis of UAIH, location of UAIH, clinical symptoms at diagnosis and treatment).

RESULTS

Nine of 22 centres responded and a total of 38 patients with UAIH were included during the 9-year period. Nine dermatologists and 2 otolaryngologists participated in this study. The mean ± SD annual number of IH seen per centre was 261.6 ± 174.7. During the study period, the total number of IH seen in all centres was 21,190 and the prevalence of UAIH was therefore evaluated at 179.3/100,000 IH.

Of these 38 patients, there were 31 girls (81.6%) and 7 boys (18.4%) whose characteristics are detailed in Table I. A total of 11 children had a past medical history, with prematurity being the most frequent event (n=5, 13.2%). This prematurity was always mild (35 or 36 weeks of amenorrhea), except for one child (32 weeks and 5 days). With regards to family history, only one child had a familial history of cutaneous IH (mother). Mean ± SD birth weight was 3,214.29 ± 532.2 g. Five (13.1%) had at least one criteria of PHACES syndrome (anomaly of the posterior fossae of the brain, arterial anomalies, cardiac anomalies, eye anomalies, sternal defect) in addition to cutaneous IH.

All but one patient were treated by oral propranolol with a mean ± SD duration of 9.7 ± 7.5 months. At the time of the study, 12 patients were still on propranolol. Clinical outcome was favourable for all children.

With regards to UAIH, mean ± SD age at diagnosis was 2.56 ± 1.7 months. A total of 18 patients was diagnosed with UAIH after presenting with only a respiratory sign (respiratory distress (n=12), mild respiratory symptom (n=6)), 9 patients had only cutaneous IH and the remaining patients (n=9, 2 missing data) had both respiratory and cutaneous manifestations.

The location of airway IH was laryngeal for 29 (76.3%) of them, pharyngeal for 6 (15.8%) and mixed (laryngeal and pharyngeal) for 3 (7.9%).

A cutaneous or mucosal location of IH was found in 31 (81.6%) of the 38 children with UAIH (Table SI[1]). The face was involved in the majority of patients (25 patients, 81%) and the distribution was segmental in 23 of them. A neck location (anterior, lateral or posterior) was found in 23 patients (74.2%). Segmental lip involvement was present in 20 patients (64.5%) (lower or both lower and upper lip, but not isolated upper lip involvement). Intra-oral location was observed in 14 patients and was always associated with lip involvement in a continuous pattern. Of these 31 cutaneous or mucosal IH, the location was considered at high risk for UAIH for 21 patients (67.7%) (Table SI[1]: patients 1–21). All had either an involvement of the neck (n=4), the lower lip (n=5), or both neck and lower lip (n=12). Of these 21 patients, 7 had a body involvement, of whom 3 had segmental distribution.

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Table I. *Characteristics of the 38 patients with upper airway infantile haemangiomas*

Case No./ Sex	Past medical history	Age at diagnosis, months	Criteria(s) for diagnosis	Location	Muco-cutaneous IH	Treatment, duration, months
1/F	No	ND	CIH; MRS	L; P	Yes	Pl (3*)
2/F	Pr	1.2	CIH	L	Yes	Pl (6)
3/F	S	ND	CIH; MRS	L; P	Yes	Pl (10.5)
4/F	No	2.5	ND	L	Yes	Pl (6*)
5/F	No	0.75	CIH	P	Yes	Pl (18*)
6/F	No	0.7	CIH	P	Yes	Pl (12*)
7/F	No	2.3	CIH; MRS	L	Yes	Pl (ND)
8/F	No	7.5	CIH	L	Yes	Pl (ND)
9/F	No	2.5	CIH; MRS	L	Yes	Pl (6)
10/F	FCA	1	CIH; MRS	L; P	Yes	Pl (6)
11/F	No	1.75	CIH	L	Yes	Pl (1*)
12/F	No	2.5	CIH; RD	L	Yes	Pl (12)
13/F	No	3	CIH	P	Yes	Pl (6)
14/F	No	2.5	MRS	L	Yes	C
15/M	Pr	2	RD	L	Yes	Pl (8)
16/F	MFI	1	RD	L	Yes	Pl (11)
17/F	No	1	CIH, MRS	L	Yes	Pl (40)
18/F	No	4	MRS	L	Yes	Pl (6)
19/M	No	1.9	RD	L	Yes	Pl (12)
20/F	IUGR	1	CIH	P	Yes	Pl (12)
21/F	No	0.5	RD	L	Yes	Pl (1*)
22/M	Pr; PRM	1.5	CIH	L	Yes	Pl (1*)
23/F	No	3.3	CIH; MRS	L	Yes	Pl (8*)
24/M	MFI	0.3	CIH	P	Yes	Pl (8.5)
25/F	No	3	RD	L	Yes	Pl (11)
26/F	No	5	MRS	L	Yes	Pl (12)
27/M	No	3	MRS	L	Yes	Pl (5*)
28/F	Pr; IUGR; PRM	5	MRS	L	Yes	Pl (21)
29/F	No	6	RD	L	Yes	Pl (13)
30/M	No	3.5	CIH; MRS	P	Yes	Pl (ND)
31/M	No	1.5	ND	L	Yes	Pl (9)
32/F	Pr; GD	1	RD	L	No	Pl (6*)
33/F	No	ND	MRS	L	No	Pl (6*)
34/F	GD	1	RD	L	No	Pl (20)
35/F	No	1.5	RD	L	No	Pl (12)
36/F	No	2	RD	L	No	Pl (11)
37/F	No	2	RD	L	No	Pl (7)
38/F	No	ND	RD	L	No	Pl (1*)

C: corticotherapy; CIH: cutaneous infantile haemangioma; FCA: foetal cardiac arrhythmia; GD: gestational diabetes; IH: infantile haemangioma; IUGR: intrauterine growth retardation; L: laryngeal; MFI: materno-foetal infection; MRS: mild respiratory symptoms; ND: not determined; *ongoing treatment; P: pharyngeal; Pl: propranolol; Pr: prematurity; PRM: premature rupture of membrane; RD: respiratory distress; S: seizure.

The characteristics of the remaining 10 patients (Nos 22–31) are described in Table SI[1]. Four patients (Nos 22–25) had very limited facial lesions. Patient 22 had no S3, but mild S1 involvement associated with scalp and posterior IH on the neck. Patients 23 (Fig. 2), 24 and 25 had a limited involvement of S3 of the lower lip, isolated or associated with other locations (S1 and/or neck and/or scalp). This lower lip involvement was unilateral for patient 23. The remaining 6 patients had no facial location of IH, but only neck (Nos 26, 30, 31), body (Nos 27 and 28) or an association of neck and body involvement (No. 29). With regards to a segmental distribution of body or neck lesions, only one patient had a segmental IH on the neck (No. 22).

DISCUSSION

We report here the largest cohort of UAIH published to date. This study revealed that a third of patients with cutaneous or mucosal IH do not completely fit with the established definition of the high-risk area for UAIH. In particular, some patients had a very limited segmental involvement of the lower lip and/or the neck without facial involvement. The limitation of the study is related to the retrospective design and the small number of patients affected by UAIH. This series illustrates the rarity of this disease, since only 38 UAIH were identified in 9 centres during a 9-year period. Two other similar, but smaller and monocentric, retrospective series were performed in the literature by Marianowski et al. (9) (15 UAIH during a 5-year period) or Tabatabaii et al. (10) (8 UAIH during an 8-year period). The characteristics of our population were in accordance with the literature, regarding the female predominance (81.6% in our study vs. 62.5–100% in the literature), the prematurity (absent or mild), and the presence of respiratory symptoms at diagnosis (71% in our series vs. 82% in the literature) (7). A comparison of the age of the patients is difficult since the authors reported the age either at presentation or at first clinical symptoms. In our study we reported the age at diagnosis.

The presence of PHACES syndrome in association with large facial IH and UAIH was reported in several studies (7, 11–13). Up to 50% of PHACES were associated with UAIH (5, 14). Our percentage was lower (16%), possibly because we included all UAIH (isolated or associated with cutaneous IH, without limitation for lesion size), whereas other studies only concerned large facial haemangiomas.

With regards to treatment, discussion about the duration of propranolol in our study is difficult and could be underestimated since nearly a third of patients were still under medication at the time of the study. The mean duration of treatment was longer than the product's recommendation (6 months). In the literature, longer durations were also reported for treating UAIH. Elluru et al. (15) (retrospective multicentre study including 27 children with UAIH treated with propranolol) found a median duration of treatment of 15 months (range 7–34 months). The age at the end of propranolol treatment also appears to be important. Broeks et al. (16) recommended not stopping propranolol until 15–18 months of age. In the literature, we noted that UAIH may be present without skin lesion in 50% of patients. However, our study showed a lower percentage (18.4%) (17). This difference could be explained by the composition of the experts group, which was made up of a majority of dermatologists, whereas in other studies, most of them were otolaryngologists (18–20).

Our study confirmed that UAIH are highly-associated with the classic skin pattern of IH in large segmental mandibular distribution (6, 7). Other skin patterns were also reported in the literature. Because of the rarity of the disease, it seems impossible to affirm a definite causal link between skin IH and UAIH, especially in single case reports or small retrospective series. In the series by Marianowski et al. (9), one of the 15 UAIH presented with cutaneous IH located on the left forearm and back. In the series by Tabatabaii et al. (10), one child had a large segmental femoral IH and another had a large segmental facial IH with neck involvement (incomplete description). The first case is probably fortuitous, unlike the second. Limited S3 involvement was previously described in 4 patients in the literature, but the pattern was different from that described in our study and, furthermore, all facial IH were large (> 22 cm^2). Suh et al. (21) described 2 cases with limited involvement of S3 in the preauricular area. Haggstrom et al. (7) reported 2 additional patients with involvement of the lower lip and chin. In our series, the limited S3 involvement only concerned the lower lip. This lower lip involvement seems therefore to be a very suggestive area of UAIH. With regards to this limited S3 involvement, we cannot exclude the fact that larger involvement, in a subcutaneous location, could have appeared without any treatment (7). The intra-oral involvement in association with UAIH is not well described in the series of the literature. O et al. (6) described the intra-oral involvement seen in 9 children

Fig. 2. Infantile haemangiomas in patient 23.

with a beard distribution and correlated this location with the location of UAIH. Based on our study, in which the intra-oral involvement was contiguous to skin IH, this location does not seem to be an important clinical finding for identifying high-risk patients.

Another interesting finding is the neck involvement, which, in our series, was either isolated or associated with facial involvement. This neck involvement is not always reported as part of the high-risk area for UAIH. It is part of the definition of the beard distribution by Orlow et al. (5) or belongs to the mandibular area defined by O et al. (6), but is not reported by Haggstrom et al. (7). In the previous studies, this neck involvement only concerns the anterior part, whereas in our study it could also be posterior or lateral. The posterior distribution was previously reported in a 2-month-old baby with UAIH without facial involvement but with large cutaneous IH on the scalp (22). Since neck involvement is very common in IH (20%) (23), and UAIH may occur without skin manifestation, we cannot exclude that the association between neck involvement and UAIH is coincidental. The same can be applied with regard to the body involvement. The only association with a plausible causal link probably concerns segmental IH located in the UAIH area (neck, anterior aspect of thoracic area). Similarly to patients with PHACES syndrome (24), or cutaneous IH associated with gastrointestinal IH (25), it seems that segmental cutaneous IH is related to an underlying vascular anomaly.

In conclusion, clinicians must be able to recognize high-risk classical areas associated with UAIH (large segmental mandibular IH), but also other limited suggestive areas: limited segmental involvement of the lower lip or segmental neck lesions (isolated or associated with limited facial involvement). These skin patterns must alert the clinician and lead to a thorough clinical examination looking for clinical respiratory signs in relation to possible UAIH. Finding these clinical signs must result in referring the case to an otolaryngologist to discuss a nasofibroscopy and/or propranolol treatment.

REFERENCES

1. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatr Dermatol 2008; 25: 168–173.
2. Léauté-Labrèze C, Prey S, Ezzedine K. Infantile haemangioma: part II. Risks, complications and treatment. J Eur Acad Dermatol Venereol 2011; 25: 1254–1260.
3. Kwon E-KM, Seefeldt M, Drolet BA. Infantile hemangiomas: an update. Am J Clin Dermatol 2013; 14: 111–123.
4. Rutter MJ. Congenital laryngeal anomalies. Braz J Otorhinolaryngol 2014; 80: 533–539.
5. Orlow SJ, Isakoff MS, Blei F. Increased risk of symptomatic hemangiomas of the airway in association with cutaneous hemangiomas in a "beard" distribution. J Pediatr 1997; 131: 643–646.
6. O TM, Alexander RE, Lando T, Grant NN, Perkins JA, Blitzer A, et al. Segmental hemangiomas of the upper airway. The Laryngoscope 2009; 119: 2242–2247.
7. Haggstrom AN, Skillman S, Garzon MC, Drolet BA, Holland K, Matt B, et al. Clinical spectrum and risk of PHACE syndrome in cutaneous and airway hemangiomas. Arch Otolaryngol Head Neck Surg 2011; 137: 680–687.
8. Haggstrom AN, Lammer EJ, Schneider RA, Marcucio R, Frieden IJ. Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. Pediatrics 2006; 117: 698–703.
9. Marianowski R, Le Ru Y, Hamel-Teillac D, De Prost Y, Manach Y, Rassi S. Prognosis of subglottic haemangiomas associated with facial haemangiomas in a paediatric population: a preliminary study. Acta Derm Venereol 2004; 84: 74–75.
10. Tabatabaii SA, Khanbabaii G, Khatami AR, Sharifnia SA. Characteristic and follow-up of subglottic hemangiomas in Iranian children. J Res Med Sci Off J Isfahan Univ Med Sci 2010; 15: 235–239.
11. Haggstrom AN, Garzon MC, Baselga E, Chamlin SL, Frieden IJ, Holland K, et al. Risk for PHACE syndrome in infants with large facial hemangiomas. Pediatrics 2010; 126: e418–426.
12. Youssef JS, Quraishi HA. Cervicofacial hemangioma and its association with PHACE syndrome. Otolaryngol Head Neck Surg 2003; 128: 758–760.
13. Alsuwaidan SN. PHACES syndrome in association with airway hemangioma: First report from Saudi Arabia and literature review. Ann Thorac Med 2012; 7: 44–47.
14. Durr ML, Meyer AK, Huoh KC, Frieden IJ, Rosbe KW. Airway hemangiomas in PHACE syndrome. The Laryngoscope 2012; 122: 2323–2329.
15. Elluru RG, Friess MR, Richter GT, Grimmer JF, Darrow DH, Shin JJ, et al. Multicenter evaluation of the effectiveness of systemic propranolol in the treatment of airway hemangiomas. Otolaryngol Head Neck Surg 2015; 153: 452–460.
16. Broeks IJ, Hermans DJJ, Dassel ACM, van der Vleuten CJM, van Beynum IM. Propranolol treatment in life-threatening airway hemangiomas: a case series and review of literature. Int J Pediatr Otorhinolaryngol 2013; 77: 1791–1800.
17. Lyons M, Vlastarakos PV, Nikolopoulos TP. Congenital and acquired developmental problems of the upper airway in newborns and infants. Early Hum Dev 2012; 88: 951–955.
18. Phipps CD, Gibson WS, Wood WE. Infantile subglottic hemangioma: a review and presentation of two cases of surgical excision. Int J Pediatr Otorhinolaryngol 1997; 41: 71–79.
19. Choa DI, Smith MC, Evans JN, Bailey CM. Subglottic haemangioma in children. J Laryngol Otol 1986; 100: 447–454.
20. Rahbar R, Nicollas R, Roger G, Triglia J-M, Garabedian E-N, McGill TJ, et al. The biology and management of subglottic hemangioma: past, present, future. The Laryngoscope 2004; 114: 1880–1891.
21. Suh K-Y, Rosbe KW, Meyer AK, Frieden IJ. Extensive airway hemangiomas in two patients without beard hemangiomas. Pediatr Dermatol 2011; 28: 347–348.
22. Mendiratta V, Varghese B, Chander R, Parakh A, Solanki RS. Successful management of airway hemangioma with propranolol. Int J Dermatol 2013; 52: 750–752.
23. Léauté-Labrèze C, Prey S, Ezzedine K. Infantile haemangioma: part I. Pathophysiology, epidemiology, clinical features, life cycle and associated structural abnormalities. J Eur Acad Dermatol Venereol 2011; 25: 1245–1253.
24. Nabatian AS, Milgraum SS, Hess CP, Mancini AJ, Krol A, Frieden IJ. PHACE without face? Infantile hemangiomas of the upper body region with minimal or absent facial hemangiomas and associated structural malformations. Pediatr Dermatol 2011; 28: 235–241.
25. Drolet BA, Pope E, Juern AM, Sato T, Howell B, Puttgen KB, et al. Gastrointestinal bleeding in infantile hemangioma: a complication of segmental, rather than multifocal, infantile hemangiomas. J Pediatr 2012; 160: 1021–1026.