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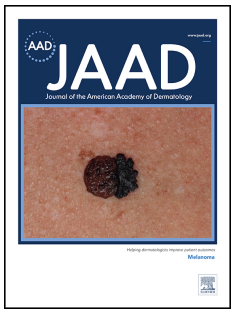

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Propranolol response in patients with segmental *vs.* focal facial hemangiomas. A retrospective case-control study

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About 10% of infantile hemangiomas (IH) are located on the face. They can be subdivided into focal (FFH) and segmental facial hemangiomas (SFH). SFH are confined to anatomically defined segments and are frequently associated with cerebrovascular[1] and other anomalies; patients with definite or possible PHACE syndrome have SFH-diameters >5 cm.[2] Since their proliferative phase is longer, SFH frequently require extended periods of treatment.[3] Length of oral propranolol therapy (OPT) required by patients with SFH *vs*. FFH and their respective relapse rates (RR) have not been studied systematically before.

In a retrospective case-control study we analyzed 52 patients with SFH and 108 age-matched patients with FFH (**Table I**) who had received OPT and were followed up in three-monthly intervals until final remission. IH were classified as superficial (no subcutaneous involvement; SFH: 48%/FFH: 31%), mixed (42%/40%), or deep (predominant subcutaneous component, 10%/29%) independently by both authors; discrepant results (<10%) were re-evaluated by a third expert. SFH-patients were divided into those with definite (15/52, 29%) or possible (2/52, 4%) PHACE syndrome and those not fulfilling current PHACE criteria[1] (35/52, 67%). All patients received 2.0-2.5 mg propranolol per kg body weight per day during an initial course of 6 months, with monthly dose-adjustments. Treatment was continued as long as there was objective evidence of growth or relapse as assessed by standardized photographs, and permanently discontinued when there was no regrowth 3 months after discontinuation.

Total duration of OPT was significantly longer in patients with SFH (382 *vs*. 190 days), and their RR was significantly higher (OR 11.4; 95%-CI 4.9 – 26.9). 20% of SFH-patients required OPT for more than 2 and up to 5.5 years (**Figure 1**). Duration of OPT and RR were independent from initial IH size, sex, or SFH subgroups, respectively. Limitations of our study are its retrospective and monocentric study design.

According to current recommendations, most children with complicated IH receive an OPT course of 6-8 months.[4] Segmental morphology, head and neck location, and subcutaneous involvement are known risk factors for persistence and relapse of IH.[3] Our results are in accordance with previous studies where children with SFH/PHACE had RRs of 32-74%, and required OPT for a median of 71 weeks.[4-5] Specific recommendations for the length of OPT in children with SFH based on real-life data would thus be helpful.

Our results indicate that 80% of children with SFH achieved recurrence-free remission after a total of 23.3 months (FFH: 6.8 months) of OPT (dotted lines in **Figure 1**). We thus recommend to treat children with SFH initially for two years. The mechanisms underlying persistent proliferation and high RR of SFH are incompletely understood.[3, 5] Further studies are needed to assess whether 24 months of continuous OPT are better than the current practice to retreat, after an initial OPT phase of 6-12 months, only upon recurrence. We hypothesize that longer and continuous suppression of IH growth by OPT might be more effective to permanently mitigate the growth potential of IH stem cells, and thus to prevent recurrences in a substantial proportion of SFH patients.

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Table and Figure

Table I

Table I: Patient characteristics and details of oral propranolol therapy in children with focal (FFH) *vs.* segmental facial hemangiomas (SFH)

	FFH	SFH	
Parameters	*n=108*	*n=52*	*p*
Female sex [no. (%)]	76 (70.4)	32 (61.5)	*0.264[b]*
Preterm [no. (%)]	17 (15.7)	4 (7.7)	*0.170[b]*
Median Diameter of IH [mm (range)][1]	14 (3-60)	40 (15-125)	*<0.001[c]*
Ulceration [no. (%)]	3 (2.8)	12 (23.1)	*<0.001[b]*
Oral Propranolol therapy (OPT) [days, range]			
Median age at initiation	94 (30-392)	54 (21-1389)	*<0.001[c]*
Mean total duration of OPT	190 (140-539)	382 (174-1988)[a]	
Mean age at last dose of OPT	296 (207-778)	525 (206-3955)[a]	
Median follow-up period after initiation of OPT	348 (260-1771)	1098 (278-3675)	
Relapse Rate[3] [no (%)]			
Patients with relapses	10 (9.3)	28 (53.8)	*<0.001[b]*

If more than one course of OPT was required, all days on therapy were added up. In case of ongoing therapy, the 31st of January 2021 was defined as last countable date. Relapse was defined as regrowth ≥ 4 weeks after completion of the last OPT course, requiring restart of OPT. [a]including 5 patients with ongoing OPT after completion of 1st course of OPT. [b]Chi-Quadrat-test. [c]Mann-Whitney-U-test. SFH-patients partially overlap with those previously reported in a study on cerebrovascular anomalies[1]

Legend to Figure 1

Figure 1: Total Duration of OPT in patients with FFH *vs*. SFH (Kaplan-Meier-Plot).

Dotted lines: The horizontal (black) line indicates that only 20% of patients remain on therapy. For patients with FFH (blue dotted line), this is the case after 204 days (6.8 months), for patients with SFH (red dotted line) after 693 days (23.3 months)
OPT: Oral propranolol therapy. SFH: Segmental facial hemangioma. FFH: Focal facial hemangioma. Comparison of survival curves with log-rank (Mantel-Cox) test (*p<0.001*).