Dermatology Practical & Conceptual

Infantile Hemangioma and Cardiac Defects: a Puzzling Association. A Single-center Experience

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ABSTRACT

Objectives: to evaluate clinical chart of patients with IH who had cardiologic evaluation before propranolol therapy and to compare our findings with literature data.

Introduction: Some studies have assessed the incidence of heart defects in children suffering from infantile hemangioma (IH) treated with propranolol, showing a possible higher prevalence of cardiac abnormalities in this group of patients.

Methods: We retrospectively reviewed clinical charts of children with infantile hemangiomas referred to our dermatologic division from 2016 to 2021, who underwent our pediatric cardiology protocol screening before starting propranolol therapy.

Results: A total of 60 infants were enrolled. Electrocardiograms were available for all the patients and echocardiography for 50/60 (83.3%) children. Electrocardiogram didn't reveal any alterations in most cases (pathologic in 2/60 ones, 3.3%) while echocardiograms revealed findings in 31/50 (51.7%) patients. Of these, persistent foramenovale, which was found in 14/50 patients (28%), was considered as non-pathologic. Interatrial septal defects were the main pathological finding in 15/50 patients (30%), as single defect or in association with other abnormalities.

Conclusions: Our study confirms the presence of a higher rate of cardiologic findings in patients with infantile hemangioma evaluated before starting oral propranolol, compared to the known rate of those defects in healthy newborns. We also confirm that interatrial septal defects are the most frequent pathologic finding with a higher prevalence compared to published studies. Large prospective studies are needed to clarify a possible association of pathological cardiac findings in all patients with infantile hemangiomas and thereafter to evaluate the possible effect of propranolol therapy on these defects during time.

Introduction

Infantile hemangiomas (IH) are the most common benign tumor in infancy with an incidence between 5% and 10% in different population [1]. Usually, they undergo a natural regression and do not require any treatment, therefore a "wait and see" approach is considered the best option for most affected newborns. However, in a subset of patients, IH can be worrisome for the risk of functional or aesthetic consequences. In 2008, following a serendipitous clinical observation, oral propranolol has been shown to be highly effective in the treatment of IH since then this drug has been widely used as galenic formulation. In 2014 an oral formulation has been licensed in Europe and oral propranolol is now considered the gold standard for the therapy of complicated hemangioma. In our hospital patients starts treatment with oral propranolol at 1 mg/kg in 2 divided doses under pediatric observation for 2 hours. The dose is then gradually increased over the subsequent weeks following the standard protocol of stepping the dose up to 2 mg/kg daily the second week of treatment and up to 3 mg/kg daily the third week. Another possibility is to follow an "at home" dose escalation strategy with telemedicine follow-up [2]. We developed and applied this protocol during the lock-down phase related to the SARS-CoV-2 pandemic, but we now offer this possibility to all families aiming to reduce the number of hospital visits. The therapy is usually continued until the 12^{th} month of life with rare exceptions, such as rapid improvement of the lesion or extensive/recurrent IH in which therapy length could be respectively reduced or prolonged.

Potential side effects of propranolol include bradycardia, hypotension, hypoglycemia, bronchospasm and sleep disturbances. All these are rare and usually not lead to discontinue the treatment [3]. Nevertheless in order to exclude congenital hidden heart disease which would contraindicate propranolol administration and to identify children in whom the drug may potentially induce side effects before starting therapy a general evaluation it is usually performed by a pediatrician. However, in our hospital, while not specifically requested in routine practice patients with IH who need propranolol therapy are also evaluated by a pediatric cardiologist [4]. Our cardiology unit offers a care package in which next to cardiologic examination also an electrocardiogram (ECG) and echocardiography (ECHO) are performed in all children.

Objectives

Few published studies have shown a raised incidence of cardiac defects in patients with IH [5,6]. We then decided to retrospectively evaluate clinical chart of patients with IH who had cardiologic evaluation before propranolol therapy and to compare our findings with literature data.

Methods

Study Population

We retrospectively evaluated clinical charts of all children with IH requiring propranolol therapy at our countryside hospital between January 2016 and January 2021. According to our protocol patients referred to our outpatient service for IH undergo a complete pediatric and cardiology evaluation including ECG and ECHOcardiogram before starting therapy. Children with segmental IH are also investigated with magnetic resonance imaging (MRI) to exclude the association with other congenital vascular malformations. Two-dimensional, M-mode, continuous Doppler and color Doppler echocardiography is performed using iE33 Philips Medical Ultrasound System equipped with a high-frequency phased-array sector scan probe (S8) and second-harmonic technology. All the evaluations are performed by the same senior cardiologist (AA) and comprise a complete sequential segmental analysis for each child. Atrial septal defect is diagnosed when a shunt through the interatrial septum can be documented by color flow mapping in subcostal four-chambers and sagittals views. We do not record as atrial septal defect (ASD) the interatrial communications less than 4 mm in length detected in infants less than 3 months of age. According to the local ethical board, informed consent was not required, since it was retrospective study with anonymous data.

Statistical Analysis

Data were analyzed by SPSS Statistics, 24.0 statistics software. Categorical variables and frequencies were compared by means of the χ^2 test or Fisher test, as appropriate. Quantitative variables were reported as median and interquartile range (IQR) and compared by means of nonparametric tests (Mann–Whitney U). A P value of 0.05 was considered to indicate statistical significance.

Results

During this study period 950 children with IH presented in our clinic. Of these, 60 (6.3%) patients with IH were treated with oral propranolol in the study frame time and all clinical charts were reviewed to retrieve relevant data. The median corrected age at first evaluation was 3 months (IQR: 2-5). Seventy percent of cases were female (42/60), and the median gestational age at delivery was of 40 weeks (IQR: 36-40). In our population, 18/60 (30%) infants were born preterm. Regarding the localization of IH, in 40/60 (66.7%) children was on the head and among these in 7/40 (17.5%) were "Cyrano" IH. 12/40 (30%) were on the scalp, 5/40 (12.5%) on the cheek (2 of these were diagnosed as

PHACE syndrome after MRI imaging), 4/40 (10%) on the ears and 12/40 (30%) on the forehead. In 9/60 (15%) IH were localized on the lower and upper arms including shoulder, 7/60 (11.7%) on the trunk, 1/60 (1.7%) on the diaper area and 3/60 (5%) presented with multiple IH. All data are summarized in Table 1.

Data about cardiologic screening in particular for ECG examination were available for all the patients and almost all (58/60, 96.7%) presented a regular ECG for age. Only 2 patients presented a right ventricular overload.

Ultrasound examination was available for 83.3% (50/60) of the patients. Among these, 19/50 (38%) didn't reveal any alterations and 14/50 (28%) had a persistent foramen ovale, a common finding considered to be non-pathological. Pooling together these two groups 33/50 patients (66%) had a normal ultrasound, while the remaining 17/50 (34%) showed significant cardiac alterations. The most frequent cardiac defect was an isolated interatrial septal defect observed in 13/17 (26% of all patients). Moreover, one patient had an interatrial septal defect associated with persistent left superior vena cava and another one associated with pulmonary stenosis. Finally, one patient had a patent ductus arteriosus and in another one a flow acceleration in the aortic arch was seen. The median age (corrected for gestational age) at which the interatrial septal defect was observed was 3 months (IQR: 2-4); 9 out of these were observed at ≥ 3 months of age (18% of all patients) and 6 at < 3month (12% of all patients). Of the 9 patients observed at ≥ 3months, 8 presented an interatrial defect > 3mm.

The median defects diameter was 4 mm (IQR: 3-6) with an ostium secundum type and left to right shunt in all patients. The 2 patients with abnormal ECG didn't present any ultrasound alterations.

A possible association of abnormal cardiac findings with demographic or clinical variables was evaluated. However, no statistically significant association was found with age (p = 0.354), sex (P = 0.757), gestational age (P = 0.480), prematurity (p = 0.329) or hemangioma localization (P = 0.494).

None of the ECG and ECHO findings were considered contraindications for systemic propranolol treatment.

Conclusions

Since systemic propranolol therapy was introduced for the treatment of IH several protocols of administration and monitoring have been proposed in order to reduce the potential risks related to the therapy [1,6]. Pretreatment evaluation is warranted both to exclude congenital hidden heart disease which would contraindicate propranolol administration and

Table 1. clinical and cardiological screening results of the study population

Characteristics	Patients (N = 60)
Age starting propranolol and cardiac screening	3 months (IQR: 2-5)
Sex (female)	42
Preterm	18
Gestational age	40 weeks (IQR: 36-40)
IH localization	
• face	40
• trunk	7
• arms	9
• diaper	1
• multiple IH	3
Cardiological findings Electrocardiogram (60/60available)	58/60 no pathologic findings
Echocardiogram (50/60available)	
• no findings	19/50
• persistent foramen ovale	14/50
• interatrial septal defect	13/50
• interatrial septal defect+ patent doctus arteriosus	1/50
• interatrial septal defect + pulmunary stenosis	1/50
• flow acceleration in aortic arch	1/50
• persistent left superior vena cava	1/50

IH = infantile hemangiomas; IQR = interquartile range.

to identify children in whom the drug may potentially induce side effects including bradycardia, hypotension, bronchospasm or hypoglycemia. Whether to perform ultrasound, ECG or simply a clinical examination is however controversial. The most recent literature underlines the lack of additional value of performing instrumental evaluations such as ECG as a pretreatment screening tool [7-11]. In our hospital a clinical protocol in which a complete pediatric and cardiologic screening, including ECG and ultrasound, is usually performed in all patients as part of a specific care package. In line with previous studies, in our population we didn't find any cardiac contraindications to start propranolol treatment. In particular ECG was performed in all the patients, but no significant findings were found thus confirming the low informative value of this exam. On the contrary some interesting data were derived from ultrasound heart examination. ECHO was available for 83.3% patients and in 38% of patients was normal. A persistent foramen ovale was found in 28% of patients and considered as a normal variant. The most frequent pathological abnormality was an interatrial septal defect that was present in 15/50 of patients (30%) either as an isolated finding (13/50 - 26%) with a presentation as ostium secundum type with left to right shunt or associated with a persistent left superior vena cava or pulmonary stenosis.

Few other studies have addressed this topic. In particular, Blei et al analyzed 239 patients and found 16% of interatrial septal defects, while Frongia et al analyzed 234 patients with only 8.1% of prevalence of this defect [5,6]. In any case, these studies clearly showed that in patients with IH there is a higher frequency of cardiac abnormalities compared with the reported incidence of congenital heart disease in the general population, which has been shown to range from 0.8% to 1.0% and going up to 7.5% only with the inclusion of other alteration such as patent foramen ovale [12-16]. Our study confirms the higher prevalence of cardiac abnormalities among patients with IH in particular of interatrial septal defect. The clinical significance of our findings is supported by the median age at observation and the median diameter of the defect which are in line with the criteria of inclusion to define congenital heart disease, ie the observation after 3 months of life and the dimension more or equal 4 mm (our median diameter was 4 mm) [17]. The 3 months age as a cut-off to consider an ultrasound finding to be relevant is because before this age the interatrial communications are common and account for 78% of the heart disease compared to 25% in older infants and children [18]. At the same time, it has been demonstrated that the incidence of spontaneous closure of interatrial communications before 3 months of age is about 60% and, in addition, interatrial defects of less than 3 mm undergo spontaneous closure in almost 100% of cases [17,18]. Our data shows that even considering only children older than 3 months (thus excluding children less than 3 months), the prevalence of ASD is anyway clearly greater than data reported in literature for general population (18% versus 0.8%-1%) [12-13].

The limited number of patients and the intrinsic limitations of retrospective studies does not allow us to draw a definitive conclusion however our study along with literature data seems to confirm that patients with IH have a substantially higher prevalence of congenital heart disease in respect to general population. Indeed, these data needs confirmation in larger prospective, multicenter, studies which should include all patients with IH to be evaluated at specific time points irrespectively of therapy with propranolol. Such a study will also be of interest to reveal a possible effect of propranolol therapy on the closure of ASD and also the significance and the possible value of IH as a clue to suspect the presence of a cardiac defect. In particular it would be of great importance to understand whether along with well-known syndromes such as PHACE a particular combination of characteristics such as dimension, number and or localization could indicate a raised risk of cardiac disease [19].

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