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Propranolol Monotherapy in Multifocal/Diffuse Infantile Hepatic Hemangiomas in Indian Children: A Case Series

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Introduction: **Infantile hepatic hemangioma (IHH) is the most common benign liver tumor in children, and multifocal and diffuse tumors often become life-threatening, necessitating therapy. Propranolol is now considered the first choice of therapy with ample data in Caucasian children. We present a series of nine Indian children with multifocal (n = 5) and diffuse (n = 4) IHH treated with propranolol monotherapy.** ***Methods:*** **This was a retrospective clinical data-based single-center study. Propranolol was used at a median dose of 3.2 mg/kg/day (range 3–3.3 mg/kg/day) for a median duration of 12 months (range 6–32 months).** ***Results:*** **The presentations of IHH (either in isolation or combination) were hypothyroidism in six patients (diagnosed by elevated serum TSH levels), heart failure in three (diagnosed based on clinical and echocardiographic features), and imaging evidence of macrovascular shunting in two patients. A good response to propranolol monotherapy (with a median dose of 3.2 mg/kg/day for a median duration of 12 months) was observed in eight patients, with a poor response in one. One patient experienced recurrence but responded adequately to propranolol retreatment.** ***Conclusions:*** **Our data reiterate the excellent response (88.9% responded) and safety profile with propranolol monotherapy in complicated IHH and strengthen the data in Asian (Indian) children. It includes the maximum proportion of complicated IHH treated with propranolol in East and South Asia, and the largest series from India. (J Clin Exp Hepatol xxxx;xxx:xxx)**

Infantile hepatic hemangioma (IHH), with its focal, multifocal, and diffuse varieties, is the most common benign liver tumor in childhood.[1] Multifocal/diffuse IHH is often of clinical concern, as they may not involute and maybe associated with complications such as consumptive hypothyroidism, heart failure (HF), micro/macrovascular shunting, and abdominal compartment syndrome.[2] Propranolol, based on existing evidence, is the first-line treatment at present replacing corticosteroids, interferon, and vincristine.[3,4] Propranolol induces vasoconstriction, resulting in anti-angiogenesis and apoptosis, and achieves a response of >95% with doses of 2–3 mg/kg/day.[3,4] Reports of the therapeutic efficacy of propranolol in children from East and South Asia, including India, are scarce.[5–7] We herein report our experience of the clinical spectrum of multifocal/diffuse IHH in a series of nine Indian children, along with the therapeutic response to propranolol in them.

METHODS

This retrospective clinical data-based study was performed at the School of Digestive and Liver Diseases, Institute of Post Graduate Medical Education & Research, Kolkata, India. All infants/children with multifocal/diffuse IHH managed between January 2014 and February 2022 were included in this study. Our database of childhood chronic liver disease, which included clinical, demographic, serological, radiological, and therapeutic details, served as a retrospective data source. Ultrasonography was the baseline imaging done in these patients, with the diagnostic criteria being hypoechoic or hyperechoic round-shaped nodules in the liver with sharp well-defined margins, a homogenous appearance and without any hypoechoic rim of compressed tissue. Diagnostic criteria on computed tomography (CT) scans were the presence of hypodense nodules with well-defined margins, gradual centripetal enhancement in delayed images, and prominent hepatic

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Abbreviations: ACS: abdominal compartment syndrome; ASD: atrial septal defect; BW: birth weight; CECT: contrast-enhanced computed tomography; HF: heart failure; IHH: infantile hepatic hemangioma; IPGMER: Institute of Post-Graduate Medical Education & Research; LBW: low birth weight; LLD: largest lesion diameter; MRI: magnetic resonance imaging; PDA: patent ductus arteriosus; TSH: thyroid stimulating hormone
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artery with postceliac narrowing of the aorta (when present). On magnetic resonance imaging (MRI), diagnosis was based on the finding of T1 hypointense/T2 hyperintense well-defined homogenous spherical lesions with sharp outlines. For the diagnosis of hypothyroidism, the cutoff value used for TSH was >10 μIU/ml (and <0.9 ng/dL for free-T4). Propranolol was initiated at a dose of 1 mg/kg/day in 2–3 divided doses and escalated in 1 mg/kg increments (till standard dosage was reached) every 3–5 days based on tolerability. Safety was ensured by monitoring the patients as inpatients till full doses were reached. Outcomes were imaging based and documented as resolved (complete involution of lesions), decreased (clinically silent but radiologically persistent), and nonresponsive (static or increased lesions).[8] This study was approved by the Institutional Ethics Committee for Human Research, which, given the retrospective record based nature of the study, granted waiver of the written informed consent requirement. However, written informed consent was also taken from the parents to use the data of the children and publish it for scientific purposes in an anonymized manner.

RESULTS (CASE PRESENTATIONS)

Case 1presented with hepatomegaly, anemia and constipation since 2 months of age, with cutaneous hemangiomas (perineum, leg) being present since one month age. MRI revealed diffuse IHH (Figure 1). She had anemia (Hb 7.3 gm/dL) and hypothyroidism (TSH >100 μIU/ml; free-T_4 1.6 ng/dL). Response was noticed after 1 week of starting propranolol (and levothyroxine) therapy by a reduction in liver size, largest lesion diameter on imaging, and TSH levels (Figure 1). The lesions did not recur off-therapy. Case 2 presented with hepatomegaly at 2 months age, which was preceded by the detection of a scalp hemangioma since 2 weeks of age. She also had anemia (Hb 5.6 gm/dL), a high TSH (>100 μIU/ml), and low free-T4 (0.47 ng/dL). Imaging (ultrasonography/MRI) revealed diffuse IHH. Lesion regression and a euthyroid state were attained after 1 year of propranolol and levothyroxine therapy. Recurrence was however noted at 10 months off-therapy, requiring retreatment with propranolol for another 10 months. The lesions again regressed and became nonprogressive during the subsequent follow-up. Case 3, who

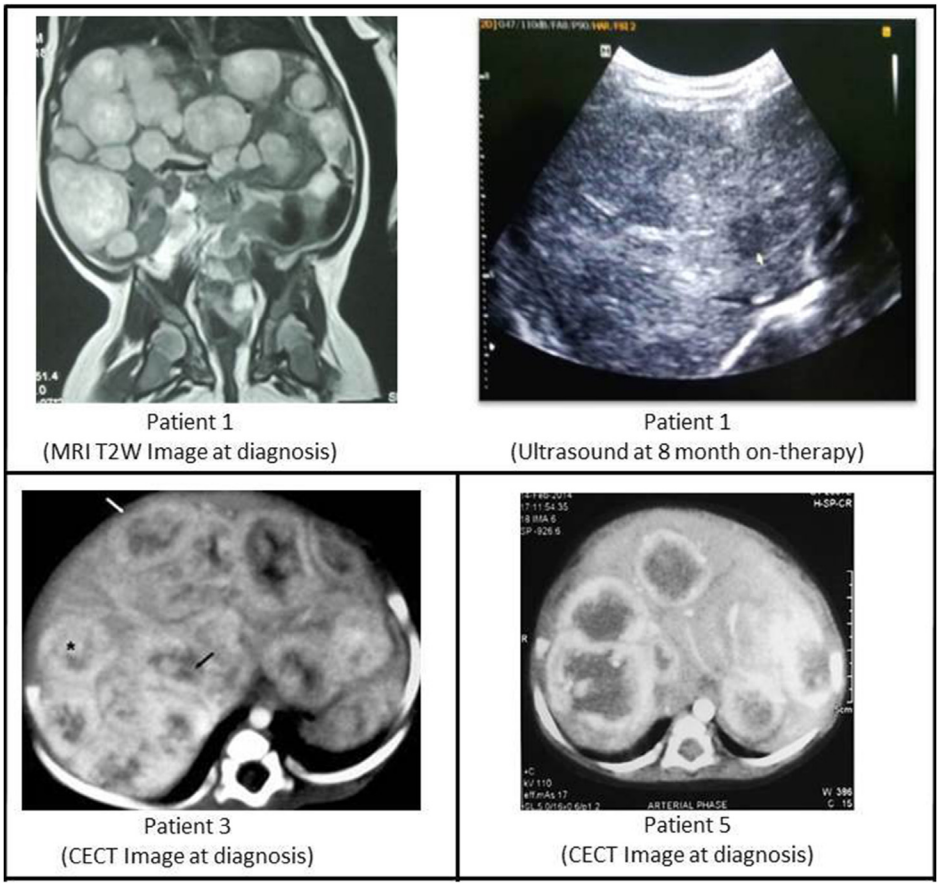

Figure 1 Selected representative images of IHH lesions from the reported patients. MRI, magnetic resonance imaging; CECT, contrast enhanced computed tomography.

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was born preterm (at 36 weeks) with low birth weight (LBW), presented with anemia, hepatomegaly, a single cutaneous hemangioma (leg), and patent ductus arteriosus (PDA) [2.5 mm, with a left-to-right shunt] with features of HF at 2 months of age. Investigations revealed anemia (Hb 6.3 g/dL), hypothyroidism (TSH >40 μIU/ml, free-T4 0.9 ng/dL), and diffuse IHH with macrovascular shunting on contrast-enhanced computed tomography (CECT) (Figure 1). Treatment with propranolol, levothyroxine, and furosemide led to a decrease in lesion size and number, a euthyroid state, and control of HF. IHH lesions were asymptomatic and nonprogressive till 4.5 years of age. She subsequently also underwent a device closure for her PDA. Case 4, having a right leg hemangioma since birth, presented to us with hepatomegaly and features of HF at the age of 6 weeks. CECT revealed diffuse IHH with evidence of macrovascular shunting. She had low albumin level (3 g/dL), high TSH level (>40 μIU/ml) and low-normal free-T4 (0.8 ng/dL). After starting propranolol, she suffered transient apnea (she had a concomitant mild respiratory tract infection at that time too). It was managed in the intensive care unit, and propranolol could be restarted at a lower dose, with a subsequent slower escalation to the maximum tolerated dose. The IHH lesions and HF responded to therapy, with a sustained off-therapy response till last follow-up at the age of 3 years. Cases 5 and 6 were anemic (Hb 8.1 gm/dL and 3.6 gm/dL, respectively) at presentation, with the former having associated cutaneous lesions and hypothyroidism (TSH 36 μIU/ml; free-T4 0.8 ng/dL) too. Cases 7 and 8 were term LBW babies. Case 7, though symptomatic since 3 months of age, presented to us at 2 years of age with HF and an associated atrial septal defect (ASD) with a left-to-right shunt. Although her HF improved with medical management, her IHH lesions did not. Case 9: a 10.5-year-old boy presented with severe upper abdominal pain (he had lower limb cutaneous hemangioma detected at birth). CECT showed multifocal IHH and intramascular arteriovenous malformations in the left anterior abdominal wall. He had high TSH level (40 μIU/ml) with normal free-T4 (0.9 ng/dL). IHH lesions regressed after 1 year of propranolol therapy and remained nonprogressive off-therapy at 2-year follow-up. However, his levothyroxine needed to be continued. All nine patients received propranolol. Drug treatment was well tolerated in all (except transient apnea in one, as mentioned), and everyone had a favorable response except for Case 7 (unchanged lesion size). A summary of clinical presentation, treatment, and outcome of all nine cases have been presented in Table 1.

DISCUSSION

The present case series of multifocal/diffuse IHH non-Caucasian children (n = 9) adds to the scarce data available from Asian countries. Moreover, we report clinical pattern and response to propranolol monotherapy in a series of patients which include a higher number of diffuse IHH and a higher prevalence of clinically relevant complications like hypothyroidism and HF, in comparison to the other Asian reports.[6,7] A recent case series from China had exclusive diffuse variety in only 2 out of 13, hypothyroidism in 3 out of 13, and HF in 1 out of the 13 reported IHH patients.[7] In another older series of 42 children from China, only two had mild hypothyroidism (none needed levothyroxine), three had HF, and the treatment offered in the 12 symptomatic patients were prednisolone, vincristine or propranolol (n = 6 for propranolol).[6]

In our series, the median age at symptom onset was 2 months (range 0.5–124), median age at diagnosis was 4 months (range 1.5–124). Prevalence of prematurity and LBW were 11% and 33%, respectively, and presence of malnutrition (Weight Z score < -2) was 33% at presentation. The female predominance (77.8%) and prevalence of hypothyroidism in our cases corroborate the reported literature.[8,9] Hypothyroidism, called consumptive hypothyroidism in such cases, occurs due to the overproduction of type 3 iodothyronine deiodinase by the tumor tissue, which converts active thyroid hormone into its inactive form, and the greater the tumor burden, the more the chances of developing hypothyroidism.[10] In our patients, the requirement for levothyroxine was found to decrease with a reduction in IHH burden while on propranolol therapy. Most patients who responded to propranolol therapy were euthyroid at the end of therapy and maintained euthyroid state without supplementation providing support to the pathophysiological link between IHH and hypothyroidism.[10] Median off-therapy follow-up was 32 months in our patients.

Most patients presented with hepatomegaly (Table 1). Six patients had associated cutaneous hemangioma with fewer than five lesions providing exception to the standard guidelines recommending screening for IHH in children with five or more cutaneous hemangioma (Table 1). Hence, the presence of hepatomegaly might be regarded as an indication for screening for IHH even in the absence of five or more skin lesions.[6,11] Three patients had HF and two had congenital heart disease (CHD) in the form of PDA in one and ASD in one. Presence of macrovascular shunting in two patients out of three with HF suggests a combined role of shunting and CHD in HF in IHH. Both patients with evidence of macrovascular shunting belonged to the diffuse variety. The diffuse variety also had a relatively larger median diameter of the largest lesion than the multifocal variety [3.7 cm (range 2.3–4) for diffuse IHH; 2.5 cm (range 1.6–8) for multifocal IHH].

Finally, out of nine patients, four resolved, four had decreased lesions, and one had static lesion size at the last visit. All tolerated the therapy well. Therapeutic response

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Table 1 Clinical Characteristics and Therapeutic Detail of Individual Cases.

Cases	1	2	3	4	5	6	7	8	9
Clinical characteristics									
Age of presentation, sex	4 mo/F	2.5 mo/F	3 mo/F	1.5 mo/M	3 mo/F	6 mo/F	2 yr/F	5 mo/F	10 yr/M
Age at symptom onset	2 mo	2 mo	2 mo	1 mo	0.5 mo	3 mo	3 mo	1 mo	10 yr
Mode of Presentation	Hepatomegaly	Hepatomegaly	Hepatomegaly	Hepatomegaly	Hepatomegaly	Hepatomegaly	Hepatomegaly	Hepatomegaly	Pain abdomen
IHH type	Diffuse	Diffuse	Diffuse	Diffuse	MF	MF	MF	MF	MF
Cutaneous hemangiomas, number	2	1	1	4	3	0	0	0	4
Hypothyroidism	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Heart failure/CHD	Absent	Absent	Present	Present	Absent	Absent	Present	Absent	Absent
Macrovascular shunting (imaging)	Absent	Absent	Present	Present	Absent	Absent	Absent	Absent	Absent
Predominant treatment indication	Hypothyroidism	Hypothyroidism	Hypothyroidism	Hypothyroidism	Hypothyroidism	Severe anemia	Heart failure/CHD	From remote area	Pain abdomen
Pre-therapy size of largest lesion (cm)	4	3.8	3.6	2.3	8	6.8	1.7	2.5	1.6
Management and outcome									
Size of the largest lesion (cm):									
a) On therapy (8 wk)	2.85	3.6	2.8	1.5	4.0	5.2	1.4	2.3	1.0
b) On therapy (6 mo)	0.84	1.1	2.2	0.7	2.1	2.8	2.5	1.1	1.3
Reduction in LLD after 6 mo Rx (%)	79	71	39	70	74	59	0	56	38
Maximum dose of propranolol used (mg/kg/day)	3.3	3.2	3.0	3.3	3.2	3.0	3.2	3.0	3.0
Propranolol therapy duration (mo)	9	13	7	32	24	6	12	6	12
End of therapy response	Resolved	Tumor size reduced	Tumor size reduced	Resolved	Resolved	Tumor size reduced	No response	Tumor size reduced	Resolved
Off-therapy Follow-up (mo)	33	41	41	8	39	0	14	0	32
Recurrence	No	Yes[§]	No	No	No	No	NA	No	No

Imaging included ultrasound followed by contrast-enhanced CT abdomen; Propranolol dosage was titrated assessing the tolerability; F: female; M: male; mo: months; yr: years; wk: weeks; IHH: infantile hepatic hemangioma; MF: multifocal; No: number; CHD: congenital heart disease; LLD: largest lesion diameter; Rx: treatment; NA: not applicable

[§]Responded to retreatment with propranolol.

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to propranolol was achieved with a median dose of 3.2 mg/kg/day for a median duration of 12 months corroborating with the literature showing >95% response with doses of 2–3 mg/kg/day (Table 1).[4,12] Recurrent lesion was also responsive to propranolol retreatment. Nonresponse in multifocal IHH possibly reflects the biology of the tumor, showing growth beyond infancy in a tenth.[13] Our therapeutic plan extended the treatment beyond one year of age to avoid the risk of rebound growth as reported in the literature.[14] Case reports of sirolimus (an angiogenesis inhibitor) use in IHH have been recently published, both in combination with propranolol and also for propranolol failure cases.[15] We did not consider it as a therapeutic option due to its higher cost and a good response to propranolol monotherapy. Despite having risk factors predicting high mortality such as diffuse variety and HF, none of our patients died.[2] We cannot provide any statistical relevance for our observations because of the small number of cases; rather, it can contribute to strengthening the data in favor of propranolol monotherapy in IHH in Asian (Indian) children.

In summary, we report that propranolol monotherapy is safe and effective both for multifocal/diffuse IHH and its complications like hypothyroidism and HF in Asian (Indian) children. These data represent the largest series of IHH from India, and one with a higher proportion of clinically relevant complications among the other published Asian reports.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Gautam Ray: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft, review and editing.

Kausik Das: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – review and editing. **Avik Sarkar:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – review and editing. **Debarshi Bose:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – review and editing. **Prasenjit Halder:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – review and editing.

CONFLICTS OF INTEREST

None.

FUNDING

None.

ETHICS APPROVAL

This study was approved by the Institutional Ethics Committee (IEC) for Human Research (Memo no: IPGME&R/IEC/2022/077, dated 05.03.2022).

CONSENT TO PARTICIPATE

Written informed consent was obtained from the parents.

CONSENT FOR PUBLICATION

The authors affirm that the parents/guardians provided informed consent to publish the data and images of their children in an anonymized manner.

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APPENDIX A

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2023.02.005.

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