diagnosis. In most cases with suspected CMPA, the diagnosis needs to be confirmed or excluded by an allergen elimination and challenge procedure [3]. This can be performed as open, single-, or double-blind challenge. Seum specific IgE, skin prick test and radio-alergosorbent assay are some of the tests available for IgE mediated CMPA. No confirmatory laboratory test is available for non IgE-mediated CMPA. Nevertheless, an oral challenge test is necessary in most cases to confirm an adverse reaction to cow's milk protein and then to make a diagnosis of CMPA. A biopsy is not needed to confirm the diagnosis unless there are very severe or overlapping symptoms.

Non IgE-mediated food allergies are known to be associated with enterocolitis syndrome (Food protein-induced enterocolitis), enteropathy, enteritis, proctitis and proctocolitis [4]. Neonatal appendicitis, as noted in this child, is a rare finding, and needs to be recognized as another manifestation of the wide spectrum of presentation of CMPA.

Contributors: AS: analyzed the case, drafted the manuscript, collected references; JM: analyzed the case and operated on the case.

Funding: None; *Competitive interests*: None stated.

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Consumptive Hypothyroidism Due to Diffuse Hepatic Hemangiomas Treated With Propranolol Therapy

Infantile hepatic hemangioma (IHH)-related consumptive hypothyroidism is rare and occurs as a result of excess thyroid hormone inactivating enzyme, type-3 iodothyronine deiodinase. We present an infant with IHH-related hypothyroidism, in whom treatment with propranolol led to regression of tumor and subsequent euthyroid status.

Keywords: *Liothyronine, Management, Type 3 deiodinase.*

Consumptive hypothyroidism is a complication of infantile hepatic hemangioma (IHH) caused by increased expression of type-3 deiodinase enzyme in the tumor tissue. This enzyme causes increased degradation of T4 and T3 to reverse T3 (inactive metabolite). When this exceeds the rate of synthesis of these hormones, a state of hypothyroidism ensues. Definitive therapy for the hemangioma and reduction in tumor burden leads to resolution of hypothyroidism. We describe a child who presented with severe hypothyroidism secondary to consumption by an IHH.

A 3-month-old female baby presented with severe constipation for the past one month. Parents also complained of dullness, poor cry and abdominal distention. There was no history of poor feeding, umbilical hernia or jaundice. The child had been born at term to a primigravida mother with a birth-weight of 2.2 kg. Her weight at presentation was 4.5 kg –2 SD) and length 55 cm (–2 to –3 SD). Physical examination revealed pallor, depressed nasal bridge and macroglossia. Her abdomen was distended and liver palpable 6 cm below the costal margin. She had an ejection systolic murmur. The thyroid gland was normally palpable.

An abdominal ultrasound revealed multiple hypoechoic lesions in the liver. Contrast-enhanced CT scan showed these lesions to have early enhancement with persistence in delayed phase consistent with a diagnosis of IHH (***Fig.* 1 a**). The child was not found to have any cutaneous hemangiomas. Thyroid function tests showed high TSH >75 mIU/L (0.57–5.54), low-normal FT4 14.6 pmol/L (60-160) and low T3 <0.62 nmol/L (1.3-2.8) (***Web Table* I**). Thyroid ultrasound showed a eutopicaly located gland and thyroid scan showed normal radionuclide uptake. Reverse T3 levels were raised (607 ng/dL, normal range 10-50) pointing towards peripheral consumption of thyroid hormone. She was

treated with oral levothyroxine 50 µg (11 µg/kg/day). However, even after two weeks, TSH remained high. Therefore, thyroxine dose was further increased. For the hemangioma, child was started on prednisolone at the dose of 2mg/kg/d. When even after 2 weeks of therapy ultrasound did not show any reduction in size of the lesion, interferon α (6 mu/m^2/day alternate day) was added. During this period the child also developed congestive cardiac failure, which was treated with digoxin and furosemide.

TSH persisted to be high even on 112.5 µg (22.5 µg/kg/day) of levothyroxine necessitating further increase in the dose to 150 µg. As the child was requiring such high doses of LT4, oral liothyronine (T3) preparation (Bitiron) was added at a dose of 12.5 µg twice a day (***Table* I**). On this dose the child remained stable with normalization of thyroid function. As ultrasound of the abdomen did not reveal any significant reduction of the tumour mass on interferon alpha therapy, it was discontinued and propranolol was started (2 mg/kg/d). Over the next 3 months, there was significant reduction in tumor size and in her thyroxine requirements. Her cardiac status also improved. There was no bradycardia or hypotension during therapy.

Liothyronine could be tapered and stopped after 5 months. After 10 months of propranolol treatment, repeat CT imaging showed complete resolution of tumor and propranolol was stopped (***Fig.* 1b**). Thyroxine doses were tapered and finally stopped at the age of 21 months. (***Table* I**). On follow-up until the age of two years the child remained euthyroid, with age appropriate developmental milestones, and normal liver appearance on ultrasound scans.

In IHH with consumptive hypothyroidism, supra-physiological doses of thyroxine are required to counteract the deactivation of T4 by the D3 deiodinase. As untreated or inadequately treated hypothyroidism in the first year of life can have severe consequences, like impaired neurodevelopmental outcome, aggressive treatment of babies with consumptive hypothyroidism is mandated. Most children respond to high doses of thyroxine, though addition of liothyronine to the treatment regimen has been reported to help in normalization of T3 levels and earlier restoration of euthyroidism [1]. Combined therapy may be useful in challenging cases where there is high rate of consumption of thyroid hormones.

Definitive therapy for hypothyroidism is treatment of IHH. Traditionally high dose corticosteroids have been the first line therapy [2]. However, steroids can have adverse effects and also increase the thyroid hormone requirement by inducing type-3 deiodinase activity and impair T4 to T3 conversion leading to further worsening of thyroid function. Second line therapy consisted of vincristine, interferon and cyclophosphamide [2]. Intractable cases need hepatic artery embolization, segmental resection or liver transplantation.

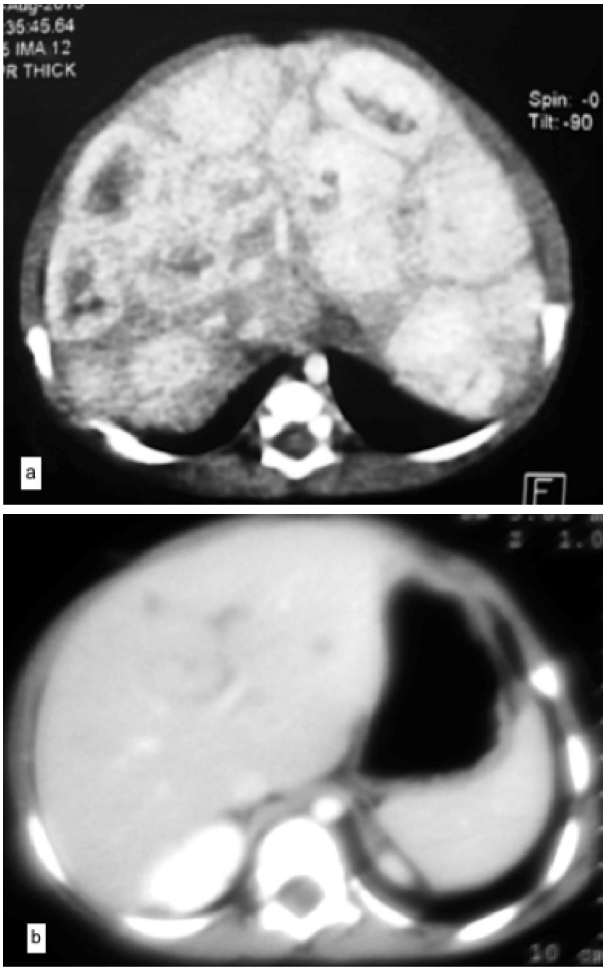

Fig. 1 *(a) Contrast-enhanced computed tomograph of abdomen in venous phase showing diffuse involvement of liver by hemagiomas, (b) Post-propanolol therapy showing complete resolution of hemagiomas.*

Propranolol was first suggested as therapy for cutaneous hemangiomas in 2008 and since then has been used for IHH as well with recent data showing a complete response in >90% patients [3-5]. Some of the proposed mechanisms of action include vasoconstriction, decreased renin production, inhibition of angiogenesis, and stimulation of apoptosis [5]. Adverse effects of the drug may be bronchospasm, bradycardia, hypotension, and hypoglycemia [3]. However, our patient did not demonstrate any of the above complications and rather showed resolution of cardiac failure.

Table I Trend of Thyroid Profile and Thyroid Hormone Requirements in the Index Case

Age (mo)	*Weight (Kg.)*	*TSH (mIU/L)*	*T4 (nmol/L)*	*T3 (nmol/l)*	*Levothyroxine dose (mcg)*	*T_3 dose (mcg)*	*Treatment For IHH*
3		>75	FT4 -14.8	<0.62 (pmol/L)	-	-	
4	4.1	-	110	0.72	75	-	Prednisolone
5 + Interferon		26.1	230	-	112.5		Prednisolone
6	5	0.44	116	<0.62	150	25	Propranolol
7		0.15	149	<0.62	100	25	
8		<0.01	136	2.51	75	12.5	
9		0.02	149	2.66	50	12.5	
11		0.068	101	2.8	37.5	12.5	
15		0.05	133	2.65	25	Stopped	
16		0.52	88	3.1	18.75	-	Stopped
18	10	1.7	126	3.1	12.5	-	
21		0.97	100	1.5	Stopped	-	
23		1.5	89	2.8	-	-	

Normal ranges: TSH:0.57-5.54 mIU/L, T_4: 60-160 nmol/L, T_3:1.3-2.8 nmol/L, FT_4: 14-31 pmol/L; TSH: Thyroid stimulating hormone.

Propranolol should possibly be offered as first line therapy to infants with diffuse IHH, especially those with hypothyroidism, as rapid normalization of thyroid function is highly desirable to ensure normal neurodevelopment.

Contributors: All authors were involved in case-management and manuscript preparation, and approved the final version of manuscript. All authors agree to be accountable for all aspects related to the study.
Funding: None; *Competing interest*: None stated.

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