CASE REPORT

Use of propranolol in a remote region of rural Guatemala to treat a large facial infantile haemangioma

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SUMMARY

We present a female infant with a right-sided facial and neck haemangioma, from a remote, resource-poor community in rural Guatemala. She received first-line treatment, propranolol, with marked reduction in tumour size and erythema. Treatment was stopped after 35 weeks due to recurrent diarrhoea and sustained weight loss. Propranolol can be used to safely treat infants with haemangiomas in remote, rural communities if there is adequate follow-up, education and communication. Periocular haemangiomas should be treated promptly to avoid visual impairment. Infants with large facial haemangiomas should be screened for Posterior fossa anomalies, Hemangioma, Arterial anomalies, Cardiac anomalies, and Eye anomalies (PHACE) syndrome, and specialists should be involved. The case also highlights the difficulty of providing treatment for a complex illness when basic health needs, such as food security and water sanitation, are limited.

BACKGROUND

An infantile haemangioma (IH) is a non-malignant vascular tumour and the most common soft tissue tumour among infants, with a prevalence of 3%–10%.^{1 2} IH incidence is higher in female, preterm and low birth weight infants.^{3 4} IHs present at birth or appear early in life as bright red macules, which can appear as solitary or multiple lesions and become raised. They tend to grow rapidly during the first year of life, and gradually involute in early childhood, usually over the course of 5 to 7 years.⁵ Haemangiomas with a deep component have an extended period of growth before involution.^{6 7}

While most IHs do not provoke symptoms, some cause marked life-threatening or functional complications, including painful ulceration and bleeding, secondary infection, airway obstruction, high-output cardiac failure and damage to surrounding tissue due to mass effect.^{3 8 9} Children with disfiguring facial haemangiomas may face social stigma.¹⁰ Periocular haemangiomas can result in visual impairment including amblyopia and astigmatism.⁹ Brief periods without visual input during the first few months of life can permanently damage the central nervous system's visual axis.⁹ Haemangiomas that obstruct the external auditory canal can result in delayed speech development.³

IHs may also be associated with syndromes such as PHACE. While PHACE syndrome is rare, it is

important to consider in infants with large facial haemangiomas, as associated anomalies may result in significant morbidity.¹¹ In a study of 108 infants with large facial haemangiomas, about one-third had extracutaneous findings consistent with PHACE syndrome.¹²

Initiating and monitoring propranolol in a rural area

Propranolol, a non-selective β -adrenergic receptor blocker, expedites the rate of involution and is well established as first-line treatment for IH and well tolerated.¹³ Patients with PHACE syndrome involving arterial disease have increased stroke risk, and therefore propranolol treatment for this subset of patients is controversial.¹¹ Initiating propranolol to treat IHs in the outpatient setting is controversial due to risk of hypoglycaemia and hypotension,¹⁴ and most reports of propranolol use in the outpatient setting are in urban areas.^{14–16} We present our concerted efforts to safely administer propranolol to treat a child with a complex IH in a remote, rural setting with limited resources with the hope that it will be useful to practitioners working in resource-poor settings.

CASE PRESENTATION

A 10-month-old girl with a large red mass involving the right side of her face, occiput and posterior neck presented to the community health post for growth monitoring in a remote, resource-poor, indigenous community in rural Guatemala. Her parents first noted a small red growth by the right corner of her mouth when she was a few weeks old. By 1 month of age, her right eye shut due to extensive growth of the mass, which soon spanned a large portion of the right side of her face with periocular involvement, part of her right ear, the occiput and her posterior neck. At times, she had painful ulceration and bleeding of the mass. She was given acetaminophen for pain, and her parents applied talcum powder to the mass without improvement. At about 4 months of age, she was seen at the nearest health centre, where her parents were not given a diagnosis and were advised to see a specialist in the capital.

Review of systems was negative for seizure activity, difficulty breathing and cyanosis or diaphoresis with exertion. Per her mother, she was born full term, with appropriate weight for gestational age, via an uncomplicated spontaneous vaginal

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Figure 1 The patient at 10 months old, immediately prior to initiating treatment (A) right profile, (B) front profile and (C) back profile.

delivery at home to a 24-year-old gravida 5 para 5 woman. Her mother did not receive prenatal vitamins or iron supplements. The patient has a history of occasional respiratory infections and diarrhoeal illnesses, but no hospitalisations or acute malnutrition.

Her family history is negative for similar lesions or masses. She has a sister with a history of acute malnutrition and a brother with severe stunting. She lives with her father, mother, four siblings, paternal grandmother, two aunts and several cousins in a compound. Her father works with livestock and agriculture. Her mother takes care of the children and cooks for the family at home. There is no electricity or potable water in her community, where food insecurity is common and experienced by her family.

Her examination was notable for raised, soft erythematous masses on the glabella and right side of her face with right periocular and right external ear canal involvement; a subcutaneous soft mass of the right lateral neck; and areas of erythematous skin with ulceration over the occiput and posterior neck (figure 1A, B, C). No other masses or skin findings were found on careful inspection. She was unable to open her right eyelids but tracked objects with her left eye, which had a normal red reflex. She responded to noises. Her heartbeat was regular rate and rhythm with normal S1 and S2. No heart murmur was appreciated. Blood pressures in all four extremities were similar and within normal limits for her age. She had normal, symmetrical and equal brachial and femoral pulses. She had no sternal defect and no visible midline defects. Her abdominal examination was normal. She had normal tone.

INVESTIGATIONS

She underwent MRI of the brain as well as magnetic resonance angiogram (MRA) of cerebral arteries, neck arteries and aorta to rule out PHACE syndrome, which refers to a large IH involving the face, neck and/or scalp with anomalies that may involve the posterior fossa, arteries, heart (such as coarctation of the aorta), eyes and sternum.¹¹ Imaging studies were notable for a 4.8 cm x 3.6 cm x 4 cm right ophthalmic mass with preseptal and post-septal components as well as a 3 cm x 4 cm x 5.5 cm mass in the right neck (figure 2A, B, C; video 1) consistent with a complex IH. The cerebral vessels, neck vessels and great vessels of the heart were patent without evidence of stenosis (video 2). We reviewed the medical literature and consulted colleagues in the USA including a paediatric vascular anomalies specialist, who provided recommendations, and a neuroradiologist, who reviewed the imaging studies.

DIFFERENTIAL DIAGNOSIS

MRI and angiography helped us to differentiate her haemangioma from vascular malformations and malignant tumours.⁹ Lymphatic malformation and rhabdomyosarcoma were considered unlikely given these conditions typically occur in older children.⁹ PHACE syndrome was ruled out based on her physical examination (normal and equal pulses and four extremity blood pressure, no murmur, no sternal defect and no abdominal raphe); brain MRI without posterior fossa abnormalities; and MRA with patent vessels of the head, neck and aortic arch.

TREATMENT

Following protocol B delineated in Drolet et al's 2013 Consensus Conference Report, we initiated treatment with propranolol at 1 mg/kg/day divided into three doses.¹⁷ The patient's pictures, at 10 months of age, immediately before initiating treatment are seen in figure 1 (A, B, C). We monitored her blood pressure and heart rate at 1 and 2 hours after the first dose, which she tolerated well. After a 24-hour observation period at our clinic and extensive counselling provided to her parents, she returned home. We stressed the importance of waiting at least 6 hours between doses, taking the medication with food, and temporarily suspending the medication when the child was ill or had decreased oral intake. Based on protocol B, her propranolol dose was increased to 2 mg/kg/day divided into three doses at a home visit and weight adjusted at monthly home visits. Since propranolol was not available at the nearest health centre or pharmacies and is not available in paediatric formulations in Latin American countries,¹⁸ our procurement and logistics specialist obtained an adequate supply of propranolol tablets, and we taught the patient's mother how to prepare a liquid suspension of propranolol.

OUTCOME AND FOLLOW-UP

Seven weeks into treatment, the haemangioma had shrunk enough for the patient to open her right eye a few millimetres. At 32.5 weeks into the treatment (figure 3A, B, C), she had marked but incomplete reduction in the tumour size and erythema. However, we began tapering her treatment at this time in the setting of recurrent diarrhoea and sustained weight loss. She had lost 1.0 kg, dropping from 8.6 to 7.6 kg over 2 months. At that time, she had a weight-for-length Z score of -1.44, and a length-for-age Z score of -2.90 consistent with moderate chronic malnutrition also known as stunting, based on the WHO's growth standards.¹⁹ The diarrhoea may have been a side effect of propranolol or infectious in aetiology and related to lack of potable water. We provided deworming medications

Figure 2 MRI brain and neck (A) T2-weighted turbo spin echo (TSE) image, coronal view; (B) T2-weighted with fluid-attenuated inversion recovery (FLAIR) image, axial view. (C) MRA brain, neck and aortic arch with gadolinium contrast, coronal view.

to the patient and her siblings as well as education about nutritional needs, water sanitation and preparation of oral rehydration solution. The patient's mother demonstrated knowledge of the quantity of food her daughter should consume, but 24-hour dietary recalls indicated that her daughter was not consistently consuming adequate quantities. This is likely related to food insecurity in her home and community, which experienced drought, has inconsistent food access, and lacks electricity and thus means of refrigeration. We provided nutritional supplementation to facilitate weight gain and prevent acute malnutrition, defined as a weight-for-length Z score less than -2.00 . Propranolol was discontinued after 3 weeks of tapering at 1 mg/kg/day. About

7 weeks after her last dose, the tumour was stable in size without evidence of rebound growth, and she no longer had diarrhoea.

DISCUSSION

To our knowledge, this is the first report of propranolol treatment for IH with follow-up occurring as home visits in a rural resource-poor setting. The Drolet *et al*¹⁷ protocol provides information for initiating propranolol in the hospital or in the outpatient setting; however, there is debate about the safety

Video 1 MRI, T1-weighted, coronal view.

Video 2 Magnetic resonance angiogram with gadolinium contrast, coronal view, f13D of the brain, neck and aortic arch showing patent vessels as well as filling of the complex haemangioma involving the right neck and orbital region.

Figure 3 The patient after 32.5 weeks of treatment when the taper was initiated (A) right profile, (B) front profile and (C) back profile.

of initiating propranolol in the outpatient setting.¹⁴ Two large prospective studies reporting safe and effective outpatient treatment of IHs with propranolol in urban environments include 697 cases in Shanghai, China,¹⁴ and 188 cases in Melbourne, Australia.¹⁵ Thirty-one patients with IHs in the large city of Tijuana, Mexico, received propranolol treatment exclusively as outpatients with follow-up provided by physicians and pharmacists.¹⁶ The scant literature about initiating propranolol in a resource-limited outpatient setting includes a case report in a resource-poor area of Indonesia.²⁰

We made concerted efforts to safely administer propranolol in a remote, rural, resource-limited setting. After 24 hours of observation at our clinic, we made home visits each month and phone calls every 2 weeks. The parents' engagement in their daughter's treatment was vital. We elicited the family's hopes and goals for treatment and involved them in shared decision making. Education was key to safely administer treatment and set reasonable expectations. Specifically, we provided counselling on propranolol's potential side effects, including hypoglycaemia and hypotension. She was monitored for symptoms of hypoglycaemia, and education was regularly reinforced via phone calls and home visits. We employed the teach-back method using oral syringes and drawings at each monthly visit to ensure her mother knew how to prepare the propranolol suspension at the weight-adjusted dose.

As many countries lack paediatric formulations of propranolol, healthcare providers in other countries have involved pharmacists or parents in preparing propranolol suspensions. In Melbourne, parents of children with IHs were given the option of dissolving propranolol tablets in water themselves or obtaining compounded propranolol syrup prepared by the pharmacy since Australia does not have licensed liquid propranolol.¹⁹ In Tijuana, Mexico, pharmacists prepared extemporaneous propranolol syrup for patients with IHs, distributed a 15-day weight-adjusted supply at a time, and provided intensive counselling and education to parents.^{16 18} Collaborating with pharmacists to prepare medication and provide education may help reduce medical errors and improve treatment response.¹⁸ In this patient's situation, collecting medications from a pharmacist every 15 days would not have been feasible because the family did not have a refrigerator or electricity and thus needed to prepare the suspension daily to prevent spoilage.

Given the risk of visual impairment, haemangiomas with periocular involvement warrant prompt attention and treatment.⁹ However, patients with large facial haemangiomas should receive advanced imaging to rule out PHACE syndrome before initiating oral propranolol, which may reduce blood

pressure and flow and thus increase the risk of stroke in patients with PHACE and stenotic vessels.¹⁷ Topical beta-blockers, which have been used in patients unable to tolerate oral propranolol and patients with residual haemangioma after a course of oral propranolol,²¹ may represent an alternative option. In systematic and meta-analyses, 72% of infants treated with topical beta-blockers (propranolol or timolol) for superficial haemangiomas had clinically significant regression without the adverse systemic effects of oral beta-blockers,²² and five patients in a case series had regression of their deep periocular haemangioma with 0.5% topical timolol gel.²³ Currently, there is lack of consensus on bioavailability and dosing of topical beta-blockers.²⁴ Through care coordination, regular and careful follow-up, caregiver education and clear communication, we were able to rule out PHACE syndrome and provide oral propranolol treatment with positive effect to an infant with a complex periocular IH in a rural area with limited health resources.

Learning points

- ▶ Propranolol can be used to safely treat infantile haemangiomas in remote rural communities through the provision of adequate follow-up, education and communication.
- ▶ Periocular haemangiomas should be treated promptly to avoid visual impairment.
- ▶ Infants with large facial haemangiomas should be screened for PHACE syndrome before initiating propranolol, and specialists should be involved.

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