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Hepatopulmonary Syndrome: An Unusual Presentation of Chronic Hypervitaminosis A

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Abstract Vitamin supplementation is a frequent phenomenon in Hong Kong children for various reasons. Vitamin A is amongst the most frequently used vitamin presented in various 'fish oil' supplements, and its toxicity is being widely reported in literature. Hepatopulmonary syndrome is a triad of chronic liver disease; increased alveolar-arterial oxygen gradient; and evidence of intrapulmonary vascular dilatation (IPVD), and has been reported in a number of liver diseases but not in hypervitaminosis A before. We reported a case in which a family of three sisters suffered from hepatopulmonary syndrome as a result of hypervitaminosis A.

Key words Hepatopulmonary syndrome; Hypervitaminosis A; Vitamin A

Introduction

Vitamin A (all-trans-retinol) is an essential fat soluble vitamin. It is involved in important processes including embryogenesis, vision, reproduction, skeletal development and maintenance of epithelial tissues.[1] It is also being frequently used in treatment of acne, as a prophylaxis against common cold, treatment for keratosis follicularis and also in treatment of malignant diseases.[2] Vitamin A has been widely used as a health supplement in developed countries. The recommended daily dosage by the US Institute of Medicine is 1000 IU for children aged one to three and 1320 IU for children aged four to eight.[3] Others recommend dosages between 1300 IU to 2300 IU depending on age and sex.[4] As a health food, it is often being taken for various reasons, including to prevent or to ameliorate symptoms of asthma.

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Due to its long half life, rapid absorption and slow clearance and the large storage capacity of liver,[5,6] toxicity could appear from an acute high dose, or, more commonly, after a prolong intake of substantially smaller doses.

Acute vitamin A toxicity can present with symptoms including anorexia, nausea, vomiting, headache, vertigo, irritability, drowsiness, lethargy, bulging fontanelle (in infants), papilloedema and pseudotumour cerebri. For chronic hypervitaminosis A, features include anorexia, weight loss, headache, intracranial hypertension, dry and scaling pruritic skin, alopecia, coarsening of hair, subperiosteal new bone growth, cortical thickening, gingival discolouration, anaemia, hepatomegaly and splenomegaly.[2,7]

Liver injury has been described in chronic hypervitaminosis A. Reported abnormalities include abnormal liver function test and mild to severe histological injuries, with hepatic stellate cell (Ito cell) hyperplasia and hypertrophy.[8] Hepatic fibrosis and cirrhosis have also been reported.[9] Less frequently described is portal hypertension without liver cirrhosis.

Hepatopulmonary syndrome (HPS) consists of a triad of chronic liver disease, alteration in pulmonary gas exchange evidenced by an increase in the alveolar-arterial oxygen pressure difference >15 mmHg while breathing room air; and evidence of intrapulmonary vascular dilatation (IPVD).[10]

A number of hepatic or portal diseases have been described to be associated with HPS. They include: alcoholic cirrhosis, postnecrotic cirrhosis, autoimmune cirrhosis, cryptogenic cirrhosis, chronic active hepatitis, primary biliary cirrhosis, biliary atresia, haemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, regenerative liver hyperplasia, post-transplant rejection and non-cirrhotic portal hypertension.[11] Hypervitaminosis A has not been described as one of the associations before.

We reported a family of four children in which three of them were receiving overdoses of vitamin A for several years, resulting in chronic liver disease with hepatopulmonary syndrome.

Case Report

A 10-year-old Chinese girl, LPY, was admitted in April 2001 due to one day history of fever, coryzal symptoms and an incidental finding of desaturation with SpO_2 82-88% in room air. She was born full term with no prenatal or perinatal problems. There was a past history of asthma with no attacks since age seven. From record, the SpO_2 was 86% in April 2000 and 90% in March 2001. On admission her weight was on 10th percentile while height was on 10-25th percentile. There was cyanosis noted with clubbing of fingers. She had no clinical signs of chronic liver disease found. Spleen tip was palpable on abdominal examination. The rest of the physical examination was unremarkable.

Complete blood picture showed decreased platelet 74 x 10^9/L, increased haemoglobin of 15 g/dL and normal white cell count. Liver function test showed increased bilirubin, 37 umol/L; renal function was normal. Chest radiogram showed normal cardiothoracic ratio of 0.49 and clear lung fields. Electrocardiogram was normal. Initial echocardiogram did not reveal structural abnormalities or pulmonary hypertension. Further contrast echocardiogram showed intrapulmonary shunt.

History revealed child's nine-year-old second sister, LKwY, was being investigated for chronic hepatitis since May 2000. No cause was found then but there was a recent onset of cyanosis. Her fourth sister, six-year-old LHY, was being investigated for thrombocytopenia and gross splenomegaly since June 2000. An ultrasound of abdomen showed coarse liver texture, suspicious of cirrhosis. The portal vein was patent with flow direction normal. There was also splenomegaly found but no ascites. The seven-year-old third sister, LKY, was well. All the three sisters have no significant past history except for mild asthma in LKwY and LHY with no attacks for several years.

Physical examination of LKwY showed no pallor, no jaundice, no cyanosis and no clubbing of fingers. Weight was 25th percentile; height was 25-50th percentile. SpO_2 was 88% in room air. Both the respiratory and the cardiovascular systems were normal. Abdominal examination showed a 9 cm spleen. No hepatomegaly was found. Other systems were normal. LKY was normal with SpO_2 99% in room air, weight 90-97th percentile and height 90-97th percentile. LHY showed a splenomegaly of 13 cm and no other abnormal signs. Her SpO_2 was 100% in air. Her weight was 50-75th percentile and height was 50-75th percentile.

Growth charts were reviewed and found there was falling off centiles of the three affected sisters. Bone marrow examination done on LHY showed erythroid hyperplasia, mild marrow eosinophilia and no abnormal storage cells. Conclusion was that the anaemia and thrombocytopenia was probably due to peripheral consumption.

Mother gave history of asthma symptoms in her children since kindergarten. They presented with chronic cough and recurrent wheezing and were given episodic oral medication by general practitioner. Due to the persistent symptoms, she began giving vitamin A and D supplement to her children since 1995 in hope of alleviating their symptoms. 80 tablets (two capfuls) a day was given instead of the recommended dosage of 1-3 tablets a day for better response. LPY and LKwY had been taking the vitamins for five years while LHY for three years. Mother has stopped giving the supplement since 2000 due to improvement of their asthma. From the infomation on the bottle, each tablet contained 10,000 units of vitamin A and 1,000 units of vitamin D respectively. Therefore the sisters were estimated of an intake of 800,000 units of vitamin A and 80,000 units of vitamin D everyday, a much higher dosage than the standard recommendations. Targeted investigations were carried out on hypervitaminosis A due to the symptoms presented. In view of the concomitant vitamin D overdose, relevant investigations were also done. Renal function and serum calcium of all the sisters were normal; urine calcium excretion was not raised. X-rays of skull and long bones showed no periosteal reaction or soft tissue calcification which could be a result from vitamin D toxicity.

Oesophageogastroduodenoscopy done in LPY and LKwY showed no oesophageal varices and biopsy showed chronic inactive gastritis with no evidence of *Helicobacter pylori* colonisation. High resolution CT thorax was done

on LPY and LKwY in view of their low oxygen saturation status, which showed generalised increase in pulmonary blood flow with increased size of vessels larger than the accompanying bronchi in all zones. There was no evidence of interstitial lung disease (Figure 1). Ultrasound of abdomen showed increased liver echogenicity consistent with cirrhosis in all three sisters, with spleen enlarged but no ascites (Figure 2). There were dilated vessels around splenic hilum suspicious of varices in LPY and LHY. Bilateral nephrocalcinosis was found in LPY and LKwY.

Cardiac assessment was done for LPY and LKwY. Intrapulmonary shunt was demonstrated by contrast echocardiography using intravenous injection of agitated saline with appearance of bubbles in the left heart chambers between the fourth and sixth beats after the injection (Figure 3).

Other haematological and biochemical laboratory tests done were shown in Table 1.

Arterial blood gas was done in LPY and LKwY, which showed an increase in alveolar-arterial oxygen pressure difference (Aa difference) which is shown in Table 2.

Liver biopsy was done on LPY in view of her more satisfactory platelet status. Result showed there were lobular

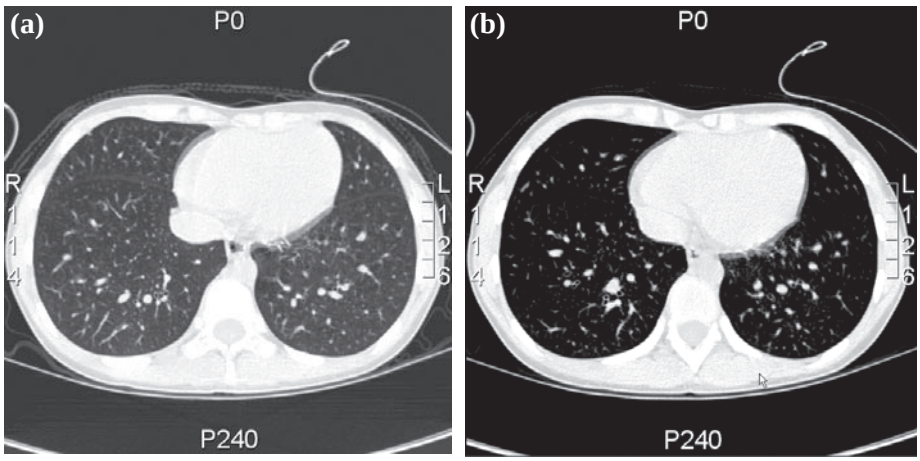

Figure 1 Contrast CT thorax of LPY, which showed diffuse dilatation of pulmonary vessels.

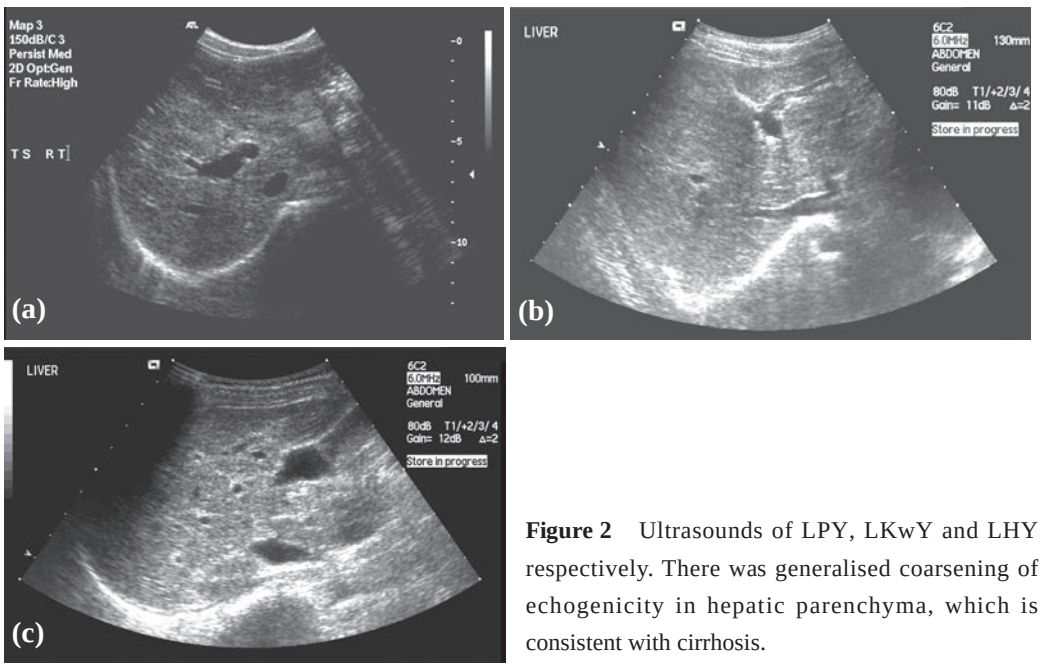

Figure 2 Ultrasounds of LPY, LKwY and LHY respectively. There was generalised coarsening of echogenicity in hepatic parenchyma, which is consistent with cirrhosis.

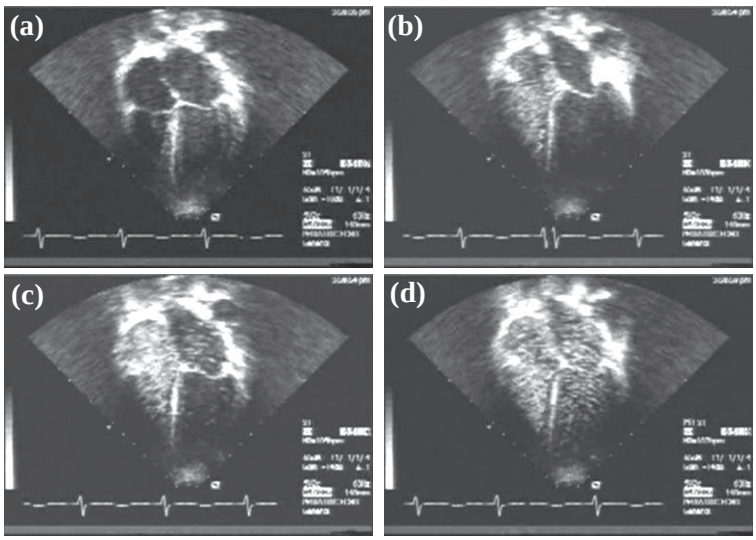

Figure 3 Contrast echocardiography of LKwY. (a) normal four chamber view, (b) immediate after injection, with dense contrast signals in right atrium and right ventricle, (c) four cycles later, bubbles entering the left atrium, (d) contrast signals in both left atrium and left ventricle while still seen in right chambers.

Table 1 Results of the three sisters in investigations of possible hypervitamnosis A

	LPY	LKwY	LHY
PT/APTT/INR	14.5s/33.9s/1.2 ↑	14.9s/38.6s/1.3 ↑	14.2/32.8/1.2
Bilirubin (umol/L)	37 ↑	43 ↑	27 ↑
Gamma GT (U/L)	28 ↑	88 ↑	
Serum Carotenoids (umol/L)	2.3 N	3.7 ↑	2.5 N
Urine Calcium Excretion (mmol/day)	2.153 ↓	0.921 ↓	1.72 ↓
Creatinine Clearance (ml/min/1.73m^2 SA)	129.88 N	260 ↑	122.58 N
Serum Copper (umol/L)	21.8 N	20.9 N	22.7 N
Serum Ceruloplasmin (mg/L)	279 N	231 N	268 N
α-1-antitrypsin (g/L)	1.74 N	1.77 N	2.01 ↑

PT: prothrombin time; APTT: activated partial thromboplastine time; INR: international normalised ratio

Table 2 Arterial blood gas showing increased alveolar-arterial gradient breathing room air

		LPY	Aa difference	LKwY	Aa difference
PaO_2kPa (mmHg)	Room air, erect	6.27 (47)	68	6.58 (50)	62
	Room air, supine	6.92 (52)	59	8.06 (60)	50
	100% oxygen, erect	13.81 (104)	N/A	32.62 (245)	N/A
	100% oxygen, supine	23.57 (177)		39.03 (293)	

and perivenule fibrosis and dilated sinusoids. Hyperplastic Ito cells were also present (Figure 4). The findings were compatible with hepatic injury due to chronic hypervitaminosis A. Quantitative assay for liver vitamin A level is not available in Hong Kong.

Vitamin A levels were done with results as shown in Table 3.

As there are no literature report that vitamin D toxicity result in damage to the liver and lung, apart from the nephrocalcinosis, it is very likely the above findings are caused by vitamin A toxicity.

Management

Dietitian was consulted for nutritional support with restriction in vitamin A consumption. In view of reversible cyanosis, LPY and LKwY were put on nocturnal oxygen to keep SpO_2 ~93% during sleep. This resulted in a subjective improvement in daytime wellbeing. The family was being referred to a liver transplant team for continuous follow up for their liver status and for any possible progression or reversibility of their condition.

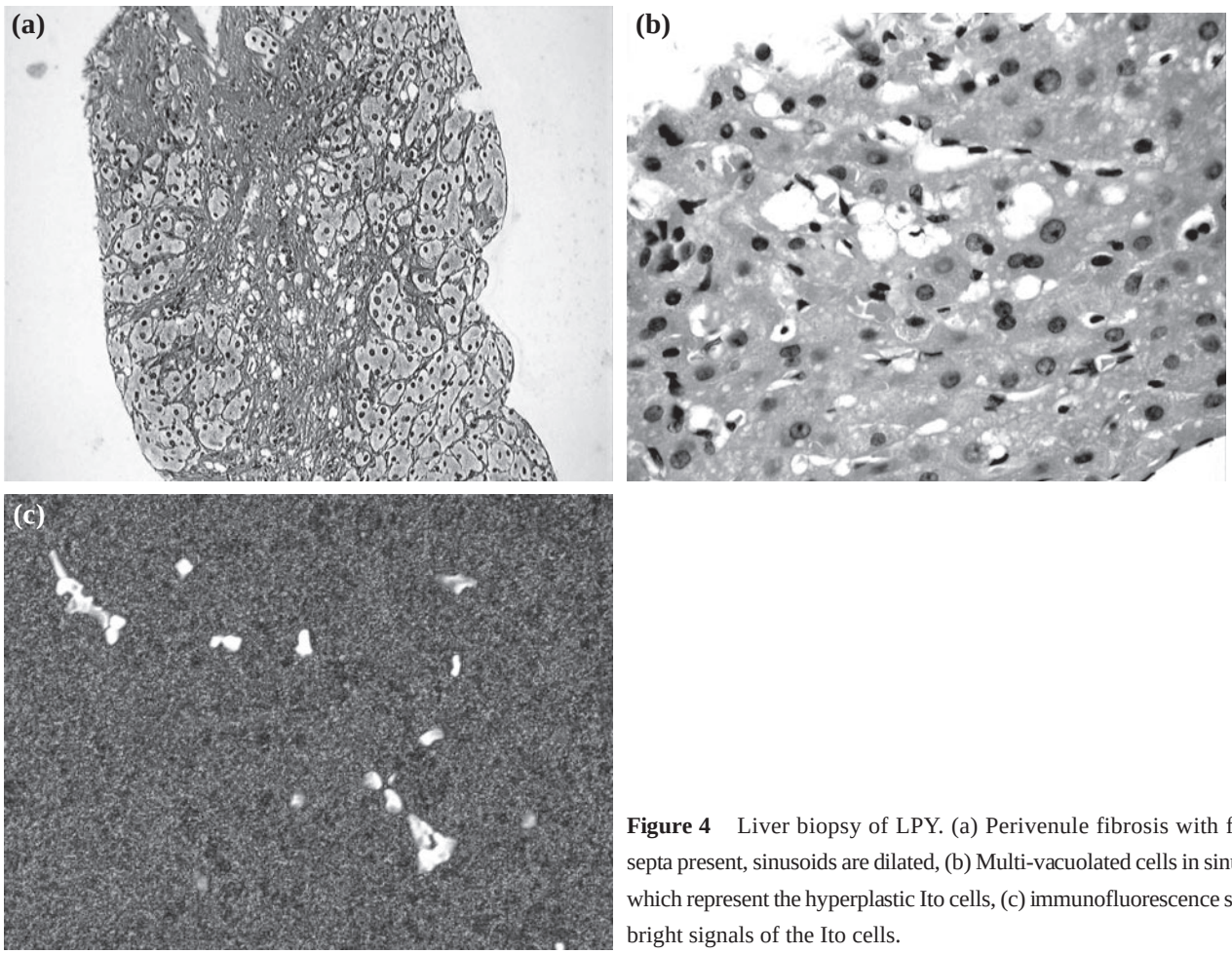

Figure 4 Liver biopsy of LPY. (a) Perivenule fibrosis with fibrous septa present, sinusoids are dilated, (b) Multi-vacuolated cells in sinusoids, which represent the hyperplastic Ito cells, (c) immunofluorescence showed bright signals of the Ito cells.

Table 3 Serum retinol (R), Retinyl palmitate (RP) and their ratios of the four sisters

	Retinol (R) (μmol/L)	Retinyl palmitate (RP) (μmol/L)	RP/R (%)
LPY	2.22	0.25	11.3
LKwY	2.11	0.47	22.3
LKY	4.65	0.12	2.6
LHY	1.88	0.16	8.5
Normal range	0.7-1.71		<6

Discussion

Our patients suffered from chronic hypervitaminosis A. From history, there was definite overdose over a period of three to five years. Though there was no report of symptoms of anorexia, nausea, vomiting or abdominal discomfort, the affected sisters suffered from decreased appetite and growth failure beginning after two years of intake.

Hepatosplenomegaly was found. Liver ultrasound showed cirrhosis and enlarged spleen. Liver biopsy performed showed changes compatible with chronic hypervitaminosis A. The serum retinyl palmitate to retinol ratio is found to be raised in the three affected sisters while normal in the child with no reported vitamin intake.

Liver damage has been reported from chronic vitamin A toxicity. In a series of 41 cases, the spectrum of vitamin A-induced liver damages ranges from increased storage found in Ito cells (stellate cell lipidosis), non-cirrhotic portal

hypertension, fibrosis, to cirrhosis.[12] Hepatopulmonary syndrome has not been reported as one of the findings.

Hepatopulmonary syndrome (HPS) is defined as a triad consisting of liver disease, pulmonary gas exchange abnormalities with increase in the alveolar to arterial oxygen gradient, and an evidence of intrapulmonary vascular dilatation in the absence of intrinsic cardiopulmonary disease.[13,14] HPS is found to be present in up to 15-20% of cirrhotic patients.[15] A number of conditions are associated with HPS, as previously mentioned.

Manifestation of HPS consists of those of underlying liver disease, which includes spider angiomas, splenomegaly, upper gastrointestinal bleeding, oesophageal varices, gastritis or ulcerations, jaundice, palmer erythema and ascites. Pulmonary symptoms of clubbing and cyanosis are also present. Dypsnoea could be present in up to 18% of cases. Platypnoea and orthodeoxia could also be present. They are defined as dypsnoea and arterial deoxygenation worsening by upright position and relieved by recumbency respectively. They are not pathogmanomas of HPS, but could be present in 88-100% of patients.[16]

The pathophysiology of this syndrome arises predominantly from diffusion-perfusion mismatch, which is caused by intrapulmonary vascular dilatations of the peripheral branches of the pulmonary artery at both pre-capillary and capillary levels (pulmonary spider naevi). Therefore it takes longer for oxygen molecules in the alveoli to diffuse to the red cells in the centre of the dilated vessels, and hypoxaemia results.[17] This could be partially overcome by increasing the partial pressures of oxygen in the alveolus, which explains the partial response to oxygen supplementation. These vascular dilatations are present in the middle to lower lung fields mostly. Therefore when moving from supine to standing, there is an increase in blood flow to the middle and lower areas of lungs by gravitational forces, making the drop in PaO_2 more pronounced, causing the platypnoea and orthodeoxia.

Various hypotheses for the cause of this vascular abnormality have been made. Most involves an imbalance between potential pulmonary vasodilators and vasoconstrictors. The pathophysiology is likely to be multifactorial. Proposed mechanisms include inability of clearance or active production of vasodilator, or the inhibition of the circulating vasoconstrictor by the damaged liver. However no one particular substance could be held responsible and the potential candidates include prostaglandins (such as prostacyclin, prostaglandin E and prostaglandin I2), vasoactive intestinal peptide, calcitonin, glucagons, substance P, nitric oxide, and atrial natriuretic factor.[18]

The most commonly used test in diagnosis of HPS is contrast echocardiography. Microbubbles, generated by agitating saline solution, are injected intravenously into the circulation. These bubbles are seen as hyperdense echo signals which enter the right heart chambers after injection. In normal situation, all the bubbles will be trapped in the pulmonary circulation and none will be seen in the left heart chambers. Intracardiac shunts will result in rapid visualisation of the bubbles in the left chambers within three heartbeats. In HPS, the bubbles pass through the pulmonary circulation, and can be seen in the left chambers on or after four heartbeats. Perfusion lung scan with technetium-labelled macro-aggregated albumin (MAA) could also be used to detect and quantify the intrapulmonary shunt. Usually the albumin will be trapped in the pulmonary vasculature resulting in complete uptake in the lungs. Finding of uptake in the brain and kidneys would indicate intrapulmonary shunting. A third method, pulmonary angiography, can be used and could structurally evaluate the pulmonary vasculature, detecting the two types of angiographic patterns in HPS. Type I pattern (microvascular shunt) consists of diffuse dilatations, and usually associated with good response to 100% oxygen. Type II pattern (macrovascular shunt) is localised vascular dilatations resembling arteriovenous communication which respond poorly to oxygen, but may respond better to embolotherapy. This method is less commonly used due to its invasiveness and is usually reserved for HPS patients with poor respond to oxygen therapy. High-resolution chest computerised tomography (CT) is an alternative method used to detect the dilated pulmonary vasculature.

Many pharmacological agents have been tried in treatment of HPS, but with no successful results so far. Almitrine bismesylate, indomethacin, octreotide, aldactone, beta-blockers, methylene blue, somatostatin, sympathomimetic agents, aspirin and garlic (allium sarivum) are amongst them.[19] Coil embolisation and transjugular intrahepatic portosystemic shunt (TIPS) are successful in case reports only.[20] Oxygen supplementation is considered as mainstay of treatment for hypoxaemic patients but data on its long term efficacy and cost-effectiveness are still lacking. Up to now, liver transplantation is the only established effective therapy for severe HPS. It could result in complete resolution of the intrapulmonary shunting and arterial oxygenation abnormalities.[21] Over 80% of patients demonstrated improvement in or resolution of the syndrome from a few

days to 15 months after orthotopic liver transplantation.[16,19] However, transplantation is not without risk. The mortality in HPS patient is up to 30% in reported series. Even though one may be cured from HPS, the patient may develop other complications from long term use of immunosuppressive therapy.[16]

There is also hypervitaminosis D in the sisters, but except from the nephrocalcinosis, there is no evidence such as hypercalcaemia, hypercalciuria, renal insufficiency or bone demineralisation found. This may be due to the fact that the supplement has been stopped for nearly 2 years when the patients first presented and therefore only the nephrocalcinosis, which is known not to resolve with cessation of overdose, remained. There is no evidence that vitamin D overdose could lead to liver or lung damage.

The reported sisters fulfill the criteria for HPS: they have liver disease due to chronic hypervitaminosis A with cirrhosis shown by USG. They have documented increased alveolar-arterial gradient by arterial blood gas measurements. Contrast echocardiography with agitated saline gave positive result of intrapulmonary shunt, and there is also no other significant cardiopulmonary disease found in the investigations done. This is, to our knowledge, the first documented case of HPS caused by chronic hypervitaminosis A.

Conclusion

Vitamin A has been used in the past for treatment of many different diseases and as a health product in prevention of diseases or in promoting general health. Acute toxicity was well documented, while chronic toxicity in moderately high doses was also reported. Chronic hypervitaminosis A is a silent killer and patients often remain asymptomatic until the disease is well advanced and irreversible. The public should be educated and warned on the sensible use on vitamin supplement. For health professionals, awareness should also be raised and enquiry on vitamin intake should be part of the history taking. For patients presenting with unexplained cyanosis, HPS should be considered especially those with chronic liver disease.

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