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ORIGINAL ARTICLE

Relation of insulin-like growth factor-1 and insulin-like growth factor binding protein-3 levels to growth retardation in extrahepatic portal vein obstruction

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Abstract
Background Growth retardation has been described in patients with extrahepatic portal vein obstruction (EHPVO). An abnormal growth hormone (GH)–insulin-like growth factor (IGF) axis has been postulated as a possible etiology. We compared anthropometric parameters and IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3) levels in patients with EHPVO with their siblings as controls.
Methods and patients Consecutive patients diagnosed with EHPVO who presented to out-patient clinic in Department of Gastroenterology between February 2005 and February 2006 were enrolled along with their siblings whenever possible. After detailed history and clinical examination, anthropometric parameters such as age, height, weight, and mid-parental height were measured in patients and controls. IGF-1 and IGFBP-3 levels were also estimated.
Results Fifty-two patients (40 males, 32 adults) were enrolled. Sibling controls were available for 28 patients. Variceal bleeding was the presenting symptom in 41 of 52 (78.8%) patients. Target height was not achieved in 7 of 32 (22.6%) adults and 6 of 20 (30%) children, showing evidence of growth retardation. The mean IGF-1 levels in patients and controls were 124.71 ± 65.49 ng/ml and 233 ± 76.98 ng/ml ($P < 0.01$), respectively. The mean IGFBP-3 levels in patients and controls were 2.90 ± 1.07 μg/ml and 4.22 ± 0.77 μg/ml ($P < 0.01$), respectively. Hormonal levels between those with and without evidence of growth retardation did not differ significantly. Duration of symptoms, spleen size, platelet count, and age of presentation did not correlate with anthropometry and hormonal levels.
Conclusions Growth retardation by anthropometry was documented in a quarter of patients with EHPVO. All patients had significantly low IGF-1 and IGFBP-3 levels in comparison with controls despite normal anthropometry in majority of patients (75%).

Keywords Portal vein thrombosis · Extrahepatic portal vein obstruction

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Introduction

Primary portal vein obstruction with cavernoma formation (extrahepatic portal vein obstruction [EHPVO]) usually presents early in life. Growth retardation has been documented in young children [1, 2]. It is not clear, however, whether they achieve their target height as per mid-parental height in adulthood (catch-up growth). Growth hormone (GH) resistance has been proposed in the causation of the decreased lean muscle mass and preserved subcutaneous fat observed in these patients; low insulin-like growth factor-1 (IGF-1) levels in the presence of high GH levels have been demonstrated [2]. A combination of IGF-1 and insulin-like growth factor binding protein 3 (IGFBP-3) has been demonstrated to be a more sensitive and specific marker for assessment of GH status [3].

We evaluated growth pattern and estimated IGF-1 and IGFBP-3 levels in patients with EHPVO.

Methods

Fifty-two consecutive patients with EHPVO who presented to the Department of Gastroenterology, KEM Hospital, from February 2005 to February 2006 were enrolled in the study. Well-nourished and healthy siblings were studied as controls. The diagnosis of EHPVO was based on the demonstration of portal cavernoma (portal vein occlusion with the presence of collateral vessels) at Doppler abdominal sonography. Patients were recruited for study at least 6 weeks after variceal obliteration and/or at least 3 months after the last bleeding episode. Patients or controls who had any cause for growth retardation (e.g., pulmonary tuberculosis, hypothyroidism) were excluded.

Complete history and other possible causes of growth retardation were investigated. This included type of delivery, birth weight, neonatal illnesses, diet, symptoms of liver dysfunction, and socioeconomic status. Detailed physical examination included looking for signs of portal hypertension, nutrition status, vitamin and mineral deficiencies, dysmorphisms, pubertal status, and any other organ system dysfunction.

Anthropometry

Anthropometric indices were measured in every patient at the first visit and at every follow-up visit. Height was measured on a wall-mounted Holtain stadiometer by one observer throughout the study period, with the patient's head held in Frankfurt plane (with the tragus in line with the outer canthus of the eye). Weight was measured on an electronic balance with digital display with a minimum division of 100 g.

Height and weight indices were plotted on growth charts (compiled by Agarwal et al.) based on anthropometry of urban Indian children. These charts provide an index of deviation from national standards in growth from birth to 18 years [4, 5]. Children who fell below the fifth percentile on the growth chart were considered to have growth retardation. The mid-parental height was calculated for all patients by adding 7 cm to the mean of parental heights in males and by subtracting 7 cm in females. This generally gives the height expected at 18 years for the child and can be plotted on the percentile chart to predict the child's height at the appropriate age. This can normally vary by 2 SDs, or 5 cm, each way [6].

Investigations

At baseline, complete hemogram and liver biochemistry were tested and an ultrasonographic Doppler examination was performed for all patients. A fasting serum sample was taken for IGF-1 and IGFBP-3 assay, which was performed by solid-phase, enzyme-labeled chemiluminescent immunometric assay (IMMULITE, Diagnostic Products, Los Angeles, CA).

Twenty-eight normal subjects who were siblings of these patients were taken as controls. Their serum was also analyzed for IGF-1 and IGFBP-3 levels.

The study protocol was approved by the institution's ethics committee and written informed consent was obtained from the patients or their parent/guardian as appropriate.

Statistical analysis

All data are presented as mean (SD). Since the reference range and age-specific values of IGF-1 and IGFBP-3 had a wide range, these values were converted to their log normal values and compared. Data were compared using unpaired *t* test. A *P* value of less than 0.05 was considered significant. The presence of growth retardation and hormonal levels was correlated with other clinical and biochemical parameters, using correlation coefficient. Data were analyzed using Epi Info (Version 3.3.2, CDC, Atlanta, GA).

Results

The 52 (40 men) patients studied had a mean age of 20 years (SD = 8.9); of these, 20 were younger than 18 years. The 28 controls (siblings of 28 patients; 20 males) had a mean age of 17.5 years (SD = 7.7); 12 were younger than 18 years. All patients had normal liver biochemistry (Table 1), and there was no evidence of liver disease clinically or at abdominal ultrasonography.

Presenting features were upper gastrointestinal tract bleeding in 41 (78.8%), left hypochondrium pain or drag in 26 (50%), anemia in 14 (26.9%), and symptoms of pancytopenia in 6 (11.5%). Four (7%) asymptomatic patients were detected incidentally on ultrasonography. WBC count was 3,000/mm^3 or less in 16 patients. Twenty patients had platelet count of less than or equal to 100,000/mm^3.

Six of the 20 patients younger than 18 years were below the fifth percentile in height. Seven of the 32 adults were short (>5 cm) in comparison with their mid-parental height.

The mean IGF-1 levels in patients and controls were 124.71 ng/ml (65.5) and 233 ng/ml (76.9), respectively. The corresponding IGFBP-3 levels were 2.90 μg/ml (1.07) and 4.22 μg/ml (0.8), respectively (Table 1).

The log normal values of both IGF-1 and IGFBP-3 in controls were significantly higher ($P < 0.01$) than in

Table 1 Insulin-like Growth Factor-1 (IGF-1) and Insulin-like Growth Factor Binding Protein-3 (IGFBP-3) levels in patients and controls

	N	Min	Max	Mean	SD
Control subjects					
Age	28	3	36	17.54	7.66
Height	28	90	184	150.15	23.93
IGF-1 (ng/ml)	28	106.0	380.0	233.00	76.98
IGF-1 (Log normal)	28	−0.718	0.89	−0.04	0.35
IGFBP-3 (μg/ml)	28	2.90	5.45	4.22	0.77
IGFBP-3 (Log normal)	28	−0.517	0.70	−0.09	0.25
Patients					
Age		6	40	20.04	8.83
Height (m)		1.03	1.80	1.51	0.19
Weight (kg)		14.0	61.5	39.23	12.97
Hemoglobin (g/dL)		5	15	9.54	2.557
Total WBC count (/cmm)		1200	16700	5359.62	3618.18
Platelets (/cmm)		22000	310000	146250.00	75886.78
Albumin (g/dl)		2.5	34.0	4.21	4.33
Spleen size at ultrasonography (cm)		9	25	16.76	4.04
IGF-1 (ng/ml)	52	25.0	392.0	124.71*	65.48
IGF-1 (Log normal)	52	−2.06	0.03	−0.78*	0.61
IGFBP-3 (μg/ml)	52	1.0	5.0	2.90*	1.07
IGFBP-3 (Log normal)	52	−1.84	0.33	−0.61*	0.45

* $P = 0.001$ as compared to control subjects

patients. IGF-1 and IGFBP-3 values were not found to be different in patients who were stunted from those having normal height for age (Table 2). Hormonal values did not correlate with age of the patient, duration of illness, and height (Table 3).

Discussion

In our study, 7 of the 32 (22.6%) adults with EHPVO were significantly shorter than their mid-parental height and 6 of the 20 (30%) patients younger than 18 years were below the fifth percentile in height. The growth charts compiled by Agarwal et al. [4, 5] are based on affluent urban children from all major zones of India evaluated between 1989 and 1991. These charts provide information on growth from birth to 18 years (unlike the new WHO standards providing data up to 5 years). At present, these charts remain the best option for growth monitoring in Indian children and are recommended for use by the Growth Monitoring Guidelines Consensus Meeting of the Indian Association of Pediatrics.

EHPVO is the most common cause of noncirrhotic portal hypertension in India [7], and it accounts for approximately 10–15% of all cases of portal hypertension [8] and almost 40% cases of portal hypertension in children [9]. Most patients present at an early age, with well-tolerated variceal bleed being the most common manifestation [7]. EHPVO results from portal vein thrombosis, but the exact etiology of this thrombosis has not been established. Umbilical sepsis is the most frequently implicated factor; in various studies, the history of sepsis is available in 0–56% of children with EHPVO [7]. We found that of 232 patients seen over 5 years, 47 had been delivered at home and 12 had history of umbilical sepsis [10].

Two studies from India have shown growth retardation in patients with EHPVO in comparison with age- and sex-matched controls [1, 2]. In the study by Sarin et al. [1], 51% of children with EHPVO had stunted growth in comparison with 16% of controls ($P < 0.01$). In the study by Mehrotra et al. [2], 18 of 33 (54.5%) patients were below the fifth percentile in height when compared with reference data derived from well-nourished Indian children.

Bellomo-Brandão et al. [11] evaluated anthropometric data obtained retrospectively from the medical records of 24 patients with EHPVO receiving sclerotherapy who had been followed up for mean 3.8 years (SD = 2.5). The mean *Z* scores at diagnosis and at the last follow-up visit were all within normal ranges when compared with the reference population. This study, however, lacked a control population. Alvarez et al. [12] showed increase in growth velocity in 25 patients who underwent successful shunt surgery for EHPVO in comparison with those in the non-operated group having similar baseline parameters.

We studied a combination of IGF-1 and IGFBP-3 for GH status. The sensitivity and the specificity of IGF-1 for diagnosing GH deficiency (with GH provocation tests

Table 2 Comparison of clinical and hormonal parameters in patients who achieved target height versus those who did not

	Achieved target height	Did not achieve target height	*P* value	Controls
Children—number	14	6		
Mean (SD) age (years)	11.46 (3.52)	12.5 (3.08)	Ns	
M:F	10:4	1:5		12:2
Age at first presentation (years)	5.71 (2.97)	4.17 (2.31)	0.2	
Duration of disease (years)	5.25 (2.80)	8.33 (3.47)	0.04	
Hemoglobin (g/dl)	8.98 (2.47)	9.17 (1.84)	Ns	
Total WBC count (/cmm)	6371.43 (5047.99)	3950.00 (2364.53)	Ns	
Platelets (/cmm)	166571.43 (81646.25)	66333.33 (20848.66)	0.009	
Albumin (g/dl)	3.74 (0.59)	3.51 (0.49)	Ns	
Spleen size at Ultrasonography (cm)	14.68 (2.96)	15.97 (2.85)	Ns	
IGF-1 Log normal	−1.1719	−0.799	Ns	
IGFBP3 Log normal	−0.818	−0.486	Ns	
Adults—number	25	7		14
Mean (SD) age, (years)	25.34 (6.60)	27.14 (8.91)	Ns	22.43 (5.85)
M:F	22:3	4:3		12:2
Mean age at presentation (years)	9.17 (3.17)	13.92 (4.25)	0.032	–
Height (m)	1.62 (0.07)	1.51 (0.15)	0.007	156.1 (5.35)*
Weight (kg)	48.30 (7.17)	39.76 (9.25)	0.014	
BMI (kg/m^2)	18.38 (2.33)	17.65 (3.98)	Ns	
Mean (SD) Duration of disease (years)	15.86 (6.28)	13.07 (5.93)	0.5	–
Hemoglobin (g/dl)	10.25 (2.65)	8.43 (2.85)	Ns	
Total WBC count (/cmm)	4912.00 (2785.13)	6142.86 (4078.34)	Ns	
Platelets (/cmm)	142960.00 (70854.00)	185857.14 (76141.16)	Ns	
Albumin (g/dl)	3.54 (0.56)	3.66 (0.42)	Ns	
Spleen size at Ultrasonography (cm)	18.34 (3.970)	15.96 (5.54)	Ns	
IGF-1 Log normal	−0.668	−0.762	Ns	
IGFBP3 Log normal	−0.685	−0.631	Ns	

IGF1: Insulin-like Growth Factor-1

IGFBP3: Insulin-like Growth Factor Binding Protein-3

* Mid-parental height

Table 3 Correlation of age, duration of illness, and mid-parental height (MPH) with hormonal values

		Age (years)	Duration of disease (years)	Height-MPH
Log normal	Correlation coefficient	−0.165	−0.223	0.054
IGFBP-3	Sig. (2-tailed)	0.243	0.112	0.771
Log normal	Correlation coefficient	0.035	−0.097	−0.100
IGF-1	Sig. (2-tailed)	0.804	0.492	0.591

being gold standard) are 80% and 65%, respectively. Combination of IGF-1 and IGFBP-3 has a sensitivity of 97% and a specificity of 95% [13, 14].

The only other study on GH assessment in EHPVO by Mehrotra et al. [2] showed a pattern of elevated GH and decreased IGF-1 levels, suggesting a state of GH resistance. We found low IGF-1 and IGFBP-3 levels, suggesting a similar mechanism. The difference in the log normal values for both IGF-1 and IGFBP-3 for patients and controls was significant; however, there was no difference in hormonal levels in patients who achieved their target height versus those who did not, suggesting that despite low IGF-1 and IGFBP-3 levels many patients achieved their target height. This lack of difference may be due to the small number of patients with growth retardation in our study. We did not estimate GH levels.

GH resistance has been documented in previous studies on adults with portal hypertension caused by cirrhosis [15, 16], as well as in children with chronic liver disease, with or without portal hypertension [17].

The cause of GH resistance in EHPVO is not known. EHPVO has been shown to result in diminished portal blood flow to the liver [18]. This has been demonstrated in cirrhotic patients to result in decreased insulin delivery to the liver [19]. Studies on an animal model of portal vein ligation have shown poor hepatic growth as well as decreased mitochondrial function during the phase of decreased hepatic blood flow [20]. GH receptor defects or impairments downstream of the receptor may thus be the cause.

The fact that three-fourths of patients in our study achieved their target height despite low IGF-1 and IGFBP-3 levels suggests that a mechanism other than GH–IGF-1 axis affects growth status in these individuals.

Our study has some limitations. We did not assess GH levels in our patients. Low levels of IGF-1 and IGFBP-3 in these patients suggest that the GH–IGF-1 axis was abnormal. Based on the results of previous studies that showed elevated GH levels in patients with EHPVO [2], it is possible that there was GH resistance in our patients as well.

In conclusion, approximately two-thirds of children and three-fourths of adult patients with EHPVO achieve their target height. The levels of IGF-1 and IGFBP-3 do not predict growth retardation in these patients, although the values in patients are significantly lower than in controls. There is a need to elucidate the role of other factors affecting growth in patients with EHPVO.

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