InTRoducTIon

Extrahepatic portal vein obstruction (EHPVO) is a vascular disorder of the liver defined by the obstruction and cavernomatous transformation of the main portal vein.\(^1\) It is characterized by noncirrhotic, presinusoidal, and prehepatic portal hypertension.\(^2\) EHPVO is the most common cause of portal hypertension and an important cause of major upper gastrointestinal bleeding in children.\(^3,4\) Although several studies, mostly from the Indian subcontinent, have documented the growth retardation in children with EHPVO,\(^5-8\) details of causes of growth failure are not clear. One study demonstrated a normal to high basal growth hormone (GH) coupled with low insulin-like growth factor-1 (IGF-1) suggesting possible GH resistance as a cause of short stature.\(^6\) Another study reported low IGF-1 and IGF binding protein-3 (IGFBP-3) levels suggesting a similar mechanism, however, GH levels...
were not estimated. IGF-1 assays have intrinsic limitations and variability subjected to age, nutritional status, and potential interference of IGFBPs. Measurement of IGFBP-3 together with the assay of IGF-1 overcomes some of these limitations, and such a combination is a more specific marker of GH status. To the best of our knowledge, none of the studies has utilized all three hormones (GH, IGFBP-3, and IGF-1) to understand the cause of short stature in these patients. Keeping in view the limitations of the above studies and utility of a combined measurement of GH, IGFBP-3, and IGF-1, the present case–control study was designed. The aim of the present study was to assess the auxological parameters and GH status (using a combination of GH, IGFBP-3, and IGF-1) in children with EHPVO. Since shunt surgery has been found to improve growth in these children, we also studied the effect of shunt surgery on these auxological parameters.

**Materials and Methods**

**Cases and controls**

Thirty consecutive children (18 boys and 12 girls) seen at a tertiary care center in North India and diagnosed to have EHPVO were enrolled in the study from May 2012 to December 2014. The diagnosis of EHPVO was based on clinical features, normal liver functions, endoscopic evidence of esophagogastric varices, and ultrasonographic findings of blocked or recanalized portal vein with the formation of portal cavernoma. The exclusion criteria included: Any other concomitant systemic disease such as tuberculosis, bronchial asthma, hypothyroidism, renal, or cardiac disease; laboratory evidence of hepatitis B or hepatitis C infection; and refusal to participate in the study. Thirty age and sex matched, well-nourished, healthy children served as controls. The controls were drawn from among the patients’ siblings or first cousins. This study was submitted to and approved by the Local Research Ethics Committee.

**Clinical workup**

A detailed general physical and systemic examination was performed in cases and controls. Height was measured on a wall-mounted stadiometer by one observer throughout the study period, with the patient’s head held in Frankfurt plane (line connecting the outer canthi of the eyes and the external auditory meatus perpendicular to the long axis of the trunk). Weight was measured on an electronic balance with a minimum division of 100 g. Height and weight indices were expressed as percentiles and standard deviation scores (SDS) calculated from growth charts described by Agarwal et al., these charts from India provide an index of deviation from national standards in growth from birth to 18 years.

**Laboratory workup**

At the baseline, detailed hemogram, urine analysis, serum biochemistry (liver and kidney function), and coagulogram were obtained in patients and controls. Hormonal workup included measurement of GH, IGF-1, and IGFBP-3 for both patients and controls. A fasting serum sample was taken for GH, IGF-1, and IGFBP-3 and samples were preserved at −30°C until processed. GH assay was done by chemiluminescence immunoassay on Beckman Coulter DXI 800, IGF-1 assay was done by RAYBIO® Human IGF-1 Elisa Kit protocol, and IGFBP-3 was done by RAYBIO® Human IGFBP3 Elisa Kit Protocol. The intra-assay and inter-assay coefficient of variation of IGF-1/IGFBP-3 assays was <10% and <12%, respectively.

**Shunt surgery**

Twelve cases underwent shunt surgery. Shunt procedures were performed by a single experienced surgeon. Proximal splenorenal shunt was performed which involved removal of the spleen with end-to-side anastomosis of the end of the splenic vein to the side of the left renal vein. In these 12 cases, we compared the growth parameters before surgery with those of 2 years after surgery.

**Results**

Thirty patients with EHPVO (18 males and 12 females) and thirty controls patients (18 males and 12 females) participated in the study. The cases and controls were similar regarding age. The mean age of cases was 12.43 ± 4.12 years and that of controls was 13.77 ± 3.02 years. Eighteen out of thirty patients had height <5th percentiles as against one in controls indicating growth retardation in 60% of the cases as against 3% in controls. Similarly, twenty out of thirty patients had weight <5th percentiles as against two in controls. The mean height SDS (HSDS) of children with EHPVO was significantly less than those of controls (−1.797 ± 1.146 for cases and −0.036 ± 0.796 for controls; P < 0.0001). Similarly, the mean weight SDS (WSDS) of children with EHPVO was significantly less than that of controls (−1.258 ± 0.743 for cases and −0.004 ± 0.533 for controls; P < 0.0001).

The mean fasting GH level was significantly higher in patients as compared to controls, (P < 0.001). Both the mean fasting IGF-1 and IGFBP-3 levels were significantly lower in patients as compared to controls (P < 0.001 for both) [Table 1]. The mean fasting IGF-1 level of cases was 100.25 ± 35.93 ng/ml while that of controls was 233.53 ± 115.06 ng/ml. Similarly, the mean fasting
IGFBP-3 levels of cases were 2976.53 ± 1212.82 ng/ml while that of controls was 5183.28 ± 1531.28 ng/ml. The growth parameters and growth-related hormone profile in patients and controls are shown in Table 1.

Of the 30 patients, 12 underwent shunt surgery. In these 12 cases, we compared the growth parameters (HSDS and WSDS) before surgery with those of 2 years after surgery. The mean HSDS significantly improved from −2.08 ± 1.31 before surgery to −1.28 ± 0.73 after surgery. The WSDS similarly improved from −1.536 ± 0.65 before surgery to −0.86 ± 0.23 after surgery.

**DISCUSSION**

EHPVO is the most common cause of noncirrhotic portal hypertension in India[16] and accounts for 40% cases of portal hypertension in children.[17] Previous studies from India have reported the growth retardation in patients with EHPVO compared with age- and sex-matched controls.[5,8] In the study by Sarin et al.,[7] 51% of children with EHPVO had stunted growth as against 16% of controls (P < 0.01). Mehrrota et al.[8] in a study of 33 patients reported that 54.5% of patients were below the 5th percentile in height. In another Indian study, more than one-third of children with EHPVO had height and/or weight Z-scores more than two standard deviations below the mean.[9] Another Indian study reported that six of the twenty (30%) patients of EHPVO younger than 18 years were below the 5th percentile in height.[9] Our results are consistent with other Indian studies. In our study, the HSDS and WSDS of cases were significantly lower than that of controls. In addition, in the present study, growth retardation was seen in 60% of our patients. Bellomo-Brandão et al.[10] in a retrospective analysis of 24 patients with EHPVO reported that EHPVO was not associated with growth impairment; however, this study lacked a control group. The comparison of our study with other studies is shown in Table 2.

The causes of growth retardation in children with EHPVO are not completely understood. Portal venous congestion of the gut, concurrent malabsorption, and anorexia from splenomegaly may contribute to poor nutrition and growth in extrahepatic portal hypertension. In a study of 11 children with prehepatic portal vein obstruction, the ability of the small gut to absorb specific monosaccharides was reduced.[19] Studies have yielded contradictory results about the role of deficient nutritional intake in these patients.[6,7]

For diagnosing GH deficiency, the combination of IGF-1 and IGFBP-3 has a markedly better sensitivity and specificity (sensitivity 97% and specificity 95%) as compared to IGF-1 alone.[10,25] Few studies have evaluated GH-IGF-1 axis in patients with EHPVO. Mehrrota et al.[9] reported a pattern of elevated GH and decreased IGF-1 levels suggesting a state of GH resistance. Another study involving 52 patients of EHPVO reported low IGF-1 and IGFBP-3 levels, suggesting a similar mechanism; however, they did not estimate GH levels.[5] In our study, we studied a combination of IGF-1, IGFBP-3, and GH. We documented high GH, low IGF-1, and low IGFBP-3 levels in EHPVO cohort compared to sex- and age-matched healthy controls. Thus, our study suggests that GH resistance is responsible for growth retardation in patients with EHPVO. GH resistance has been documented in previous studies on adults with portal hypertension caused by cirrhosis,[21,23] as well as in children with chronic liver disease, with or without portal hypertension.[22] The cause of GH resistance in EHPVO is elusive. EHPVO has been shown to result in diminished portal blood flow,[24] and this has been demonstrated in cirrhotic patients to result in decreased insulin delivery to the liver.[25] There is also evidence from animal studies that portal vein ligation leads to poor hepatic growth, as well as mitochondrial dysfunction during the phase of decreased hepatic blood flow.[26] This may result in GH receptor defect or a postreceptor signaling defect.

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**Table 1: Growth parameters and growth-related hormone profile in patients and controls**

| Parameter       | Patients | Control subjects | P value |
|-----------------|----------|------------------|---------|
| HSDS            | −1.797±1.146 | −0.036±0.796 | <0.0001 |
| WSDS            | −1.258±0.743 | −0.004±0.533 | <0.001  |
| GH (ng/ml)      | 5.00±6.46  | 1.78±2.04       | <0.001  |
| IGF-1 (ng/ml)   | 100.25±35.93 | 233.53±115.06  | 0.000   |
| IGFBP-3 (ng/ml)| 2976.53±1212.82 | 5183.28±1531.28 | 0.000   |

Data are means±SD. HSDS: Height standard deviation score; WSDS: Weight standard deviation score; GH: Growth hormone; IGF-1: Insulin like growth factor-1; IGFBP-3: Insulin like growth binding protein-3

**Table 2: Summary of main findings on EHPVO and growth parameters**

| Authors          | Year | Number | Growth retardation | GH ng/ml | IGF1 ng/ml | IGFBP3 ng/ml |
|------------------|------|--------|--------------------|----------|------------|--------------|
| Sarin et al.[7]  | 1992 | 61     | 51%                | NR       | NR         | NR           |
| Mehrrota et al.[8]| 1997 | 33     | 54.5%              | 4.60     | *          | NR           |
| Menon et al.[9]  | 2005 | 30     | 66%                | NR       | NR         | NR           |
| Nihal et al.[11]| 2009 | 52     | 30%                | NR       | 124.71     | 2900         |
| Present study    | 2016 | 30     | 60%                | 5±6.4    | 100.25±35.93 | 2976.53±1212.82 |

*Presented as Z score which were significantly lower. Unless otherwise stated, values are means±SD. EHPVO: Extrahepatic portal vein obstruction, NR: Not reported, GH: Growth hormone, IGF-1: Insulin-like growth factor-1; IGFBP-3: Insulin-like growth factor binding protein-3
Effect of shunt surgery

Twelve patients underwent proximal splenorenal shunt. In these patients, we documented a significant improvement in height and WSDS, 2 years after shunt surgery. Few studies have reported the effect of shunt surgery on growth parameters in children with EHPVO. A striking increase in growth velocity after portosystemic shunt surgery for extrahepatic portal hypertension was first reported in 1983 by Alvarez et al. In a randomized, controlled study, Kato et al. reported that children with EHPVO who underwent shunt surgery had a significant improvement in growth compared with children who did not undergo surgery. Finally, in a study of thirty children with EHPVO, 76% showed improvement in height Z-scores compared to their presurgical scores after shunt surgery.\[8\]

Conclusions

We documented that the height and weight SDSs of children with EHPVO were significantly lower than that of sex- and age-matched controls. Evaluation of GH-IGF-1 axis revealed GH resistance responsible for growth retardation in these patients. Finally, in 12 patients, who underwent shunt surgery, a significant increase in weight and height SDS was seen after shunt surgery.

Limitations

A small sample size may be a limitation, however even the sample size of sixty (thirty cases and thirty controls) was sufficient to draw the aforementioned conclusions. The strength of the study lies in complete evaluation of GH-IGF-1 axis.

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Conflicts of interest

There are no conflicts of interest.

References

1. Sarin SK, Sollano JD, Chawla YK, Amarapurkar D, Hamid S, Hashizume M, et al. Consensus on extra-hepatic portal vein obstruction. Liver Int 2006;26:512-9.
2. Gauthier F. Recent concepts regarding extra-hepatic portal hypertension. Semin Pediatr Surg 2005;14:216-25.
3. Howard ER, Stringer MD, Mowat AP. Assessment of injection sclerotherapy in the management of 152 children with oesophageal varices. Br J Surg 1988;75:404-8.
4. Sarin SK, Misra SP, Singal AK, Thorat V, Broor SL. Endoscopic sclerotherapy for varices in children. J Pediatr Gastroenterol Nutr 1988;7:662-6.
5. Nihal L, Bapat MR, Rathi P, Shah NS, Karvat A, Abraham P, et al. Relation of insulin-like growth factor-I and insulin-like growth factor binding protein-3 levels to growth retardation in extrahepatic portal vein obstruction. Hepatol Int 2009;3:305-9.
6. Mehrrota RN, Bhatia V, Dabardghao P, Yachha SK. Extrahepatic portal vein obstruction in children: Anthropometry, growth hormone, and insulin-like growth factor I. J Pediatr Gastroenterol Nutr 1997;25:520-3.
7. Sarin SK, Bansal A, Sasan S, Nigam A. Portal-vein obstruction in children leads to growth retardation. Hepatology 1992;15:229-33.
8. Menon P, Rao KL, Bhattacharya A, Thapa BR, Chowdhary SK, Mahajan JK, et al. Extrahepatic portal hypertension: Quality of life and somatic growth after surgery. Eur J Pediatr Surg 2005;15:82-7.
9. Furlanetto RW. Insulin-like growth factor measurements in the evaluation of growth hormone secretion. Horm Res 1990;33 Suppl 4:25-30.
10. Blum WF, Ranke MB. Use of insulin-like growth factor-binding protein 3 for the evaluation of growth disorders. Horm Res 1990;33 Suppl 4:317.
11. Alvarez F, Bernard O, Brunelle F, Hadchouel P, Odiere M, Alagille D, et al. Portal obstruction in children; Part II. Results of surgical portosystemic shunts. J Pediatr 1983;103:703-7.
12. Kato T, Romero R, Koutouby R, Mittal NK, Thompson JF, Schlein CL, et al. Portosystemic shunting in children during the era of endoscopic therapy: Improved postoperative growth parameters. J Pediatr Gastroenterol Nutr 2000;30:419-25.
13. Khanna R, Sarin SK. Non-cirrhotic portal hypertension - Diagnosis and management. J Hepatol 2014;60:421-41.
14. Agarwal DK, Agarwal RN, Upadhyay SK, Mittal R, Prakash R, Rai S. Physical and sexual growth pattern of affluent Indian children from 5 to 18 years of age. Indian Pediatr 1992;29:1203-82.
15. Agarwal DK, Agarwal RN. Physical growth in Indian affluent children (birth-6 years). Indian Pediatr 1994;31:377-413.
16. Sarin SK, Agarwal SR. Extrahepatic portal vein obstruction. Semin Liver Dis 2002;22:43-58.
17. Panda MK, Jain PK, Gupta S, Nihal L, Bapat MR, Rath PM. Profile of pediatric portal hypertension in a tertiary hospital in Western India. Indian J Gastroenterol 2005;24:A134.
18. Bellomo-Brandão MA, Morcillo AM, Hessel G, Cardoso SR, Servidioni Mde F, da-Costa-Pinto EA. Growth assessment in children with extra-hepatic portal vein obstruction and portal hypertension. Arq Gastroenterol 2003;40:247-50.
19. Taylor RM, Bjarnason I, Cheeseman P, Davenport M, Baker AJ, Mieli-Vergani G, et al. Intestinal permeability and absorptive capacity in children with portal hypertension. Scand J Gastroenterol 2002;37:807-11.
20. Rosenfeld RG, Wilson DM, Lee PD, Hintz RL. Insulin-like growth factors I and II in evaluation of growth retardation. J Pediatr 1986;109:428-33.
21. Shankar TP, Solomon SS, Duckworth WC, Jerkins T, Iyer RS, Bobal MA. Growth hormone and carbohydrate intolerance in cirrhosis. Horm Metab Res 1988;20:579-83.
22. Møller S, Juul A, Becker U, Flyvbjerg A, Skakkebaek NE, Henriksen JH. Concentrations, release, and disposal of insulin-like growth factor (IGF)-binding proteins (IGFBP), IGF-I, and growth hormone in different vascular beds in patients with cirrhosis. J Clin Endocrinol Metab 1995;80:1148-57.