PO Box 2345 Beijing 100023, China
Fax: +86-10-85381893
Email: wcjd@wjgnet.com www.wjgnet.com

World Chin J Digestol 2004 May;12(5):1191-1195
世界华人消化杂志 ISSN 1009-3079 CN 14-1260/R


• 文献综述 •

# 特发性门脉高压症

陈 陵, 杨仕明, 房殿春, 贾树蓉, 陈 飞, 孙浩平

陈陵, 杨仕明, 房殿春, 陈飞, 孙浩平, 中国人民解放军第三军医大学西南医院全军消化专科中心 400038
贾树蓉, 中国人民解放军第三军医大学西南医院B超室 重庆市 400038
项目负责人: 杨仕明, 400038, 重庆市高滩岩, 中国人民解放军第三军医大学西南医院全军消化专科中心. shimingyang@yahoo.com
电话: 023-68754678 传真: 023-68754124
收稿日期: 2003-10-27 接受日期: 2004-01-15

## 摘要

特发性门脉高压症临床少见，病因不明，是导致门脉高压的第二大原因. 主要表现为门脉高压、显著脾肿大伴脾功能亢进及贫血，肝功能基本正常. 病理改变主要表现为门静脉纤维化，肝内门静脉终末支破坏，以及肝实质萎缩，但无肝硬化改变. 血流动力学改变为肝内窦前性门脉高压，即肝门静脉压力显著升高而肝静脉楔压基本正常，脾静脉及门静脉血流量增加. 治疗基本与肝硬化所致门脉高压相同，预后主要取决于上消化道静脉曲张的严重程度及其处理.

陈陵, 杨仕明, 房殿春, 贾树蓉, 陈飞, 孙浩平. 特发性门脉高压症. 世界华人消化杂志 2004;12(5):1191-1195
http://www.wjgnet.com/1009-3079/12/1191.asp

## 0 引言

特发性门脉高压症(idiopathic portal hypertension，IPH)在历史上称谓众多，如班替氏综合征(Banti’s syndrome)[1]、班替氏病(Banti’s disease)[2]、良性肝内门脉高压(benign intrahepatic portal hypertension)[3]、肝门静脉硬化症(hepatoportal sclerosis)[4-5]、非硬化性门静脉纤维化(non-cirrhotic portal fibrosis，NCPF)[4-6]. 由于临床病理表现相似，很难明确区分，故目前认为是同一疾病，普遍接受的名称是IPH[5]. 其病因及发病机制长期以来知之甚少. 在发病率较高的印度和日本研究很多，我国报道很少.

## 1 流行病学

以印度与日本发病率较高，西方国家很低. 整个印度次大陆都有报道[7]，占因门脉高压而就诊患者的1/6-1/4，主要见于贫困人群，男女之比为2∶1-4∶1，发病年龄为30-35岁. 日本IPH发病率为0.75/10 000[5]，约占因门脉高压而来就诊患者的1/3，男女之比为1∶3，男、女患者平均年龄分别为44.5 ± 15.8岁和51.8 ± 11.0岁. 在美国和英国IPH患者占因门脉高压来就诊患者的3-4%，性别差异不显著. 各地IPH患者在性别和年龄分布上的差异原因尚不清楚，可能与社会经济状态、生活卫生条件、寿命长短以及种族不同有关. 我国近年也有报道，但例数较少[8]，可能是因为缺乏对本症的认识.

## 2 病因及发病机制

病因和发病机制至今仍不清楚. 最初怀疑接触有毒物质是引起IPH的重要原因. 如砷的慢性摄入可引起不同程度的肝脏损害，常见的是肝内门静脉纤维化[9]，发生率可高达91.3%[10]. 进而出现窦前性门脉高压症，无肝硬化表现. 铜中毒[11]及长期接触氯乙烯原料[12]也可能导致IPH. 6-巯基嘌呤，硫唑嘌呤等免疫抑制剂在肾移植后的应用可能是肾移植后IPH的原因[13-16]. 但也有不少学者发现没有毒物接触史的IPH患者[17]，故可能还有其他原因通过共同机制导致IPH.

腹腔内感染引起的门静脉炎症可能是IPH的发病原因之一. 研究人员将已死亡的大肠杆菌(*Escbericbia coli*)反复注射入兔与狗的门静脉内，结果在短期内出现门静脉纤维化，门静脉压力升高[18-20]. 腹腔内感染所致无症状的慢性门静脉内毒素血症可激活相关细胞因子，引起凝血功能异常，导致门脉内弥漫性血管内凝血(disseminated intravascular coagulation，DIC)，进而导致门脉纤维化，引起IPH[21]. 这些相关细胞因子可能包括结缔组织生长因子(connective tissue growth factor，CTGF)，体外可刺激成纤维细胞增长，促进细胞外基质合成，可能是引起IPH患者门脉纤维化的重要因子之一[22]. 近年印度与日本随着经济卫生条件的改善，腹腔内感染减少，IPH发病率明显下降[5,23]，间接提示感染可能是IPH病因之一.

凝血因子V的突变可能与IPH发病有关. Ishii *et al*[24]发现了1例伴凝血因子V突变的IPH患者. 现已知道这种突变可引起各处静脉内血栓形成，而门静脉内血栓形成足以引起门脉高压，且难以发现. 因而，曾一度认为肝内门静脉血栓与IPH密切相关[25-26]. 但日本学者对此提出异议，因为较大肝内门静脉分支内血栓均出现在IPH晚期[27]，因而血栓更象是IPH的结果. Okudaira *et al*[5]详细罗列了不支持血栓致IPH的依据: (1)IPH为隐袭发病，病前无任何肝内血管血栓征兆; (2)脾大并非继发于充血，因为脾静脉血流量在IPH患者中是增加的; (3)IPH患者中血液未见高凝状态; (4)对136例IPH患者行肝活检，仅发现3例有血栓形成; (5)对早期IPH患者行经肝门静脉造影术，未发现血栓; (6)一些IPH尸检病例并未发现肝内血栓.

免疫因素在IPH发病机制上越来越受到重视. 临床上观察到IPH与其他免疫性疾病如系统性红斑狼疮

(systemic lupus erythematosus，SLE)[28]、进行性全身硬化症(progressive systemic sclerosis，PSS)[29]、系统性硬化症(systemic sclerosis，SSc)[24]、桥本氏甲状腺炎(hashimoto’s thyroiditis)[30-31]、混合性结缔组织病(mixed connective tissue disease，MCTD)[32]、雷诺氏征(Raynaud’s phenomenon)[33-34]、风湿性关节炎(rheumatoid arthritis )[35]、Ⅰ型糖尿病[36]以及硬皮病(scleroderma)[37]等同时存在. 日本IPH研究委员会通过全国性调查发现69.2%的女性IPH患者抗DNA抗体阳性，24.1%抗核抗体阳性，21.5%抗线粒体抗体阳性，17.2%抗甲状腺球蛋白抗体阳性[34]. 除了这些自身抗体外，在IPH患者中还发现了许多免疫异常. 如自身混合淋巴细胞反应[38]，以及异常的T-细胞基因库[39]. Kathayat *et al*[40]采用兔的脾提取物反复致敏兔，得到非硬化性门脉纤维化的兔模型. 这个动物模型表现为巨脾，门脉压力持续升高，但肝实质未见损害，与人NCPF非常类似，提示反复免疫刺激可能在NCPF中起重要作用. Tokushige *et al*[41-42]发现，IPH患者可溶性TNF受体-2明显升高，外周血及脾内淋巴细胞Th1与Th2比率比对照组显著升高(主要是由于Th2 CD4 T细胞百分比下降)，血管细胞黏附分子-1 (vascular cell adhesion molecule-1，VCAM-1)的血清水平也升高. 他们可能都参与IPH的发病.

## 3 病理改变

IPH的病理改变为不同程度的门静脉纤维化以及门静脉硬化. 然而，IPH的这些病理改变并无特异性[27]，很可能是持续门脉血流灌流不足之后，肝细胞凋亡，肝实质损害、萎缩、纤维化[22]. 因而，IPH的肝脏病理改变依据分期不同，差异很大. (1) 大体病理: IPH患者肝实质常发生萎缩，重量一般比正常肝脏小[22]. Nakanuma *et al*[27]依据IPH患者肝脏大体及切片外观，提出如下分期系统: 第一期: 整个肝脏无萎缩，切面见肝包膜下也无实质萎缩; 第二期: 肝脏无萎缩，肝包膜下实质可见萎缩; 第三期: 肝脏萎缩，肝包膜下实质也见萎缩; 第四期: 门静脉内出现阻塞性血栓. 第一期似乎常越过第二期发展到第三期. 而第四期出现相对较晚，预后也差. 这一分期系统有助于我们理解IPH患者肝脏的形态学改变. 肝脏切面上可见门静脉主干及其肝内主要分支有显著的血管周围纤维化改变，比肝硬化明显得多. 肝内门静脉分支扩张，血管壁不同程度增厚和纤维化. 肝切面肉眼可见的肝静脉分布不规则，在肝萎缩明显处模糊不清. 一些大的肝静脉有硬化改变. 有时可见大面积缺血性坏死，可能是终末期改变. (2) 镜检: IPH肝脏没有特异的组织学改变. 组织学检查发现不仅在不同时期有差异，在同一肝脏的不同位置也有不同. Okudaira *et al*[5]总结了以下几点: (1) 门静脉主干及其肝内大分支有显著的血管周围纤维化改变，这些血管内膜增厚，并伴中层平滑肌过度增生，血管腔偶见狭窄. 而一些门静脉管腔正常，甚至扩张. 尸检病例中门静脉主干内常可见到血栓形成. 围绕胆管周围常可见同心板层状纤维化，以及大量胶原纤维及弹性纤维增生. 门静脉末梢支观察到有2种纤维化形式. 一种是IPH的特征改变，即门脉末梢支管壁纤维化伴显著管腔狭窄. 另一种是形成钉状纤维突起，向肝实质延伸，一些甚至连接到另一门脉末梢支和中央静脉. 与门脉主干及大分支相关，末梢支内极少见到血栓形成. 肝内门脉末梢支大小及数量都有减少，门脉分支常消失或被破坏，取而代之的是弹性纤维样变. (2) 中晚期病例常可见被膜下区肝实质塌陷. 肝小叶内结构常可保存，但门脉区及中央区结构紊乱. 肝内假小叶少见. (3) 在肝实质明显萎缩处可见肝静脉血管硬化及狭窄. 这可能是因为长期门静脉血流异常的结果.

## 4 血流动力学改变

脾静脉及门静脉压力显著增加. 但无肝内门体分流形成. 肝静脉楔压(wedged hepatic vein pressure，WHVP)基本正常或轻度升高，但显著低于门静脉压力(pressure of portal vein，PPV)，也比肝硬化患者低得多[43-46]. 门脉系统内血流受阻的病理解剖位置有两处. 一个在窦前，压力梯度存在于脾(脾内门脉系统压力)与肝(肝内门脉压力)，另一个在窦周，压力梯度存在于肝内门脉压力与WHVP之间[47]. 曲张静脉内压力则与肝硬化门脉高压患者相近[47-48]. 血流受阻是由于门静脉中小分支增厚和阻塞，以及迪氏腔内胶原形成[6]. 脾及门静脉明显扩张，血流量显著增加，门脉系统内血流循环呈高动力状态，肝内可有门体静脉间侧副管形成，这些侧副管的形成降低了患者曲张静脉出血的风险[4].

## 5 临床表现、诊断和鉴别诊断

依据IPH临床表现，在日本卫生福利部主持下，日本IPH研究委员会制订了IPH的诊断要点[5, 49]: (1)不明原因的脾大、贫血、门脉高压，可除外肝硬化、血液疾病、肝胆系统的寄生虫病、肝静脉及门静脉阻塞以及先天性肝纤维化等. 也就是说，IPH的临床诊断可通过排除以上相关疾病而确立. (2)一种以上血液成分减少. (3)肝功能试验正常或接近正常. (4) B超、CT或脾脏同位素检查有门静脉及脾静脉扩张，血流量增加，脾肿大. 肝表面光滑，质地均匀，无萎缩，不提示有肝硬化. (5) 内镜或X线证实有上消化道静脉曲张. (6)肝静脉插管检查显示肝静脉开放，WHVP正常或轻度升高，直接门静脉测压大于20 mmHg. (7)腹腔镜提示肝表面无肝硬化表现; 肝活检显示门脉纤维化，但无肝硬化. 并非必须具备以上每一条标准才能诊断，但是必须确有门脉高压并且可绝对排除肝硬化和其他原因引起的非肝硬化性门脉高压才可诊断.

肝外门静脉梗阻(extrahepatic portal vein obstruction，EHPVO)可通过检查门脾静脉内有无梗阻(超声，CT，造影)而与IPH轻易区分，但在门静脉主干内同时出现血栓的情况下则不易诊断. IPH大多发病隐匿，而

EHPVO 多发病急骤，可出现曲张静脉直径突然增大，胃肠道突然出血，腹痛及腹水. IPH 患者部分凝血活酶时间(partial thromboplastin time，PTT)及血中纤维蛋白原降解物水平均正常，而 EHPVO 患者二者都升高[21]. 肝硬化患者在 Child A 级时临床症状可与 IPH 类似，但肝功能、病毒学及组织学(肝小叶结构紊乱，假小叶形成)的检查易于将二者区分. 另外由于IPH肝脏外周门静脉血流灌注相对内部更少[50-51]，而肝硬化则无此特点，CT 检查中 IPH 患者在肝动脉造影时肝脏外周相对内部增强，而肝硬化则内外一致，这也有助于二者区别. 热带巨脾综合征(tropical splenomegaly syndrome，TSS)发生于热带地区，表现为巨脾. 然而，门脉高压并不常见于 TSS，WHVP 也在正常范围内[52]. 而且，TSS 患者血清 IgM 水平及疟疾抗体效价大多升高.

IPH 还可能引起一些并发症. 肝硬化门脉高压患者并发的舒张期心功能障碍，同样也可发生于 IPH[53]，原因不明. 可能与门脉高压，血浆肾素活性等有关. 肝肺综合征(hepatopulmonary syndrome，HPS) 在 IPH 患者中发生率约为 13.3%[54-55]，可使患者更易出现呼吸困难，半卧位呼吸，杵状指等. 肝性脊髓病(hepatic myelopathy)曾见于 1 例 IPH 患者[56]，表现为痉挛步态，可能与脊髓脱髓鞘或轴突损伤有关. 其他不常见的并发症还有自发性脾梗死[57]、肝衰竭[58].

## 6 治疗与预后

正确及时地处理胃肠道出血及脾功能亢进是治疗 IPH 的关键. 对急性出血病例，内镜下曲张静脉套扎术(endoscopic variceal ligation，EVL)及内镜下硬化剂治疗(endoscopic sclerotherapy，EST)非常有效，控制急性出血成功率大于 95%[59]. 为消除上消化道曲张静脉所需硬化治疗的疗程次数，IPH患者与肝硬化患者相近[60]. 治疗后曲张静脉复发率约为 20%，但再出血发生率很少，约为 3%[60-61]. 仅有不到 5% 的患者才必须行急诊分流手术[61]，术后死亡率约为 10%，术后分流道堵塞、明显的门体分流性脑病和再出血等并发症发生率大约为 10%[62-63].

对非急性出血病例，口服倍他乐克预防 IPH 所致出血与 EVL 术的疗效相当[64]. 介入放射治疗效果也很好，即便曾做过分流或断流手术也可采用[65]. 介入放射治疗包括部分脾栓塞术(partial splenic embolization，PSE)、经皮经肝曲张静脉栓塞术(percutaneous transhepatic obliteration，PTO)以及经颈静脉肝内门体分流术(transjugular intrahepatic portosystemic shunt，TIPS). Romano *et al*[66]对 6 例(2 男，4 女，平均年龄 30.3 岁)伴脾大、血小板减少和反复曲张静脉出血的 IPH 患者进行 PSE 治疗，结果发现脾容积平均缩小 68%，血小板平均增加 120 $\times$ $10^9$/L，在之后的随访中(最短 18 mo，平均 28.2 mo)，无 1 例曲张静脉再出血，未发现重大并发症，疗效持久. 外科治疗曾被报道是除内镜治疗外的有效选择[67]，尤其是内镜治疗无效、脾功能亢进伴自发性出血、严重贫血需要反复输血以及反复脾梗死者. Lytkin *et al*[68]对 14 例 IPH 患者成功地进行了外科治疗(脾肾分流术 9 例，脾切除术 3 例，脾动脉结扎术 1 例)，并进行了长达 10 a 的随访. 2 例脾肾分流术分别于术后 6 a 及 10 a 反复出血死亡，其他患者均未出现再次出血. 有 6 例行脾肾分流术患者术后 6-10 a 后出现了其他疾病(分流性脑病，肾结石，高血压，十二指肠溃疡). 这表明外科治疗虽 5 a存活尚可，但远期疗效不佳，不宜作为首选. 而且，近来还有报道在 IPH 患者外科分流术后出现膜性增生性肾小球肾炎及其他肾脏疾病[69]. 在术式选择上，一些日本及印度学者更倾向于断流术[70-72]. 与分流术相比，断流术更简单、安全，能有效控制出血，改善生活质量，并极少出现门体分流性脑病. 胃静脉曲张可见于大约 1/4 的 IPH 患者，比肝硬化患者更常见[73]. 在诊断 IPH 后平均 12.8 mo 即可出现[74]，在行食管曲张静脉闭塞术(EST，EVL)后，会出现更早. 这些曲张静脉常可经过注射氰基丙烯酸酯凝胶来治疗，很少需要外科干预[75].

IPH患者存活曲线几乎与相同年龄及同性别的普通人口类似[45]. 急性出血后死亡率明显低于肝硬化患者[71]. 在成功处理胃食管静脉曲张后，2 a 及 5 a 存活率接近 100%. 如果选择外科分流术，分流道阻塞和分流术后脑病会引起一些患者死亡，但控制蛋白质摄入可以在很大程度上改善症状. IPH女性患者可妊娠及生育[76-77]. 怀孕后最常见的并发症是曲张静脉破裂出血，可通过内镜下硬化治疗有效地处理，对母婴均很安全. 部分患者在接受以上治疗 3-10 a 后可能会出现进行性肝衰竭[58]，此时原位肝移植术将是惟一选择.

## 7 参考文献


1 Pickhardt PJ, Balfe DM. Portal vein calcification and associated biliary stricture in idiopathic portalhypertension (Banti's syndrome). *Abdom Imaging* 1998;23:180-182

2 Tokushige K, Yamauchi K, Hayashi N, Futagawa S, Hirose S, Shirai T. The pathogenesis of idiopathic portal hypertension. *Nippon Geka Gakkai Zasshi* 1996;97:21-26

3 Levison DA, Kingham JG, Dawson AM, Stansfeld AG. Slow cirrhosis-or no cirrhosis? a lesion causing benign intrahepatic portalhypertension. *J Pathol* 1982;137:253-272

4 Dhiman RK, Chawla Y, Vasishta RK, Kakkar N, Dilawari JB, Trehan MS, Puri P, Mitra SK, Suri S.Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with151 patients and a review of the literature. *J Gastroenterol Hepatol* 2002;17:6-16

5 Okudaira M, Ohbu M, Okuda K. Idiopathic portal hypertension and its pathology. *Semin Liver Dis* 2002;22:59-72

6 Sarin SK, Kapoor D.Non-cirrhotic portal fibrosis: current concepts and management. *J Gastroenterol Hepatol* 2002;17:526-534

7 Basu AK, Boyer J, Bhattacharya R, Mallik KC, Sen Gupta KP. Non-cirrhotic portal fibrosis with portal hypertension: a new syndrome I. Clinical and function studies and results of operations. *Indian J Med Res* 1967;55:336-350

8 陈加, 吴俊超, 杨锦林. 特发性门脉高压临床分析. 华西医学 2002;17:223

9 Centeno JA, Mullick FG, Martinez L, Page NP, Gibb H, Longfellow D, Thompson C,Ladich ER. Pathology related to chronic arsenic exposure. *Environ Health Perspect* 2002;110 (Suppl 5):883-886

10 Guha Mazumder DN. Arsenic and liver disease. *J Indian Med Assoc* 2001;99:311

11 Pimentel JC, Menezes AP. Liver disease in vineyard sprayers. *Gastroenterology* 1977;72:275-283
12 Thomas LB, Popper H, Berk PD, Selikoff I, Falk H. Vinyl-chloride-induced liverdisease. From idiopathic portal hypertension (Banti's syndrome) to Angiosarcomas. *N Engl J Med* 1975;292:17-22
13 Noel C, Hazzan M, Coppin MC, Bridoux F, Codaccioni MX, Pruvot FR. Idiopathic portal hypertension: an infrequent complication of renaltransplantation. *Transplant Proc* 1995;27:2437
14 Yanagisawa N, Sugaya H, Yunomura K, Harada T, Hisauchi T. A case of idiopathic portal hypertension after renal transplantation. *Gastroenterol Jpn* 1990;25:643-648
15 Nataf C, Feldmann G, Lebrec D, Degott C, Descamps JM, Rueff B, Benhamou JP. Idiopathic portal hypertension (perisinusoidal fibrosis) after renaltransplantation. *Gut* 1979; 20:531-537
16 Roland S, Delwaide J, Cornet G, Mahieu P, Jacquet N, Belaiche J. Clinical case of the month. Hepatoportal sclerosis in a patient treated withazathioprine. *Rev Med Liege* 1998;53:450-453
17 Zamora Davila E, Ramirez Mayans J, Cervantes Bustamante R, Cueva Carrillo J,Mora Tiscareno MA, Mata Rivera N, Cuevas Schacht F, Zarate Mondragon F.Hepatoportal sclerosis. 10 years of experience at the National Institute ofPediatrics. *Acta Gastroenterol Latinoam* 1997;27:49-52
18 Sugita S, Ohnishi K, Saito M, Okuda K. Splanchnic hemodynamics in portal hypertensive dogs with portal fibrosis. *Am J Physiol* 1987;252(6 Pt 1):G748-754
19 Kono K, Ohnishi K, Omata M, Saito M, Nakayama T, Hatano H, Nakajima Y, Sugita S, Okuda K. Experimental portal fibrosis produced by intraportal injection of killed nonpathogenic Escherichia coli in rabbits. *Gastroenterology* 1988;94: 787-796
20 Sugita S, Ohnishi K, Iida S, Nomura F, Okuda K. Histological changes in the liver and portal hypertension subsequent to repeated intraportal injections of killed *E.coli* in the dog. *Liver* 1988;8:1-9
21 Bajaj JS, Bhattacharjee J, Sarin SK. Coagulation profile and platelet function in patients with extrahepatic portal vein obstruction and non-cirrhotic portal fibrosis. *J Gastroenterol Hepatol* 2001;16:641-646
22 Tsuneyama K, Kouda W, Nakanuma Y. Portal and parenchymal alterations of the liver in idiopathic portalhypertension: a histological and immunochemical study. *Pathol Res Pract* 2002; 198:597-603
23 Chawla Y, Duseja A. Non-cirrhotic portal fibrosis (NCPF) is a vanishing disease in India. *Trop Gastroenterol* 2003;24:45-46
24 Ishii M, Katada Y. Idiopathic portal hypertension in a systemic sclerosis patient heterozygous for factor V Leiden mutation. *Rheumatol Int* 2003;23:44-46
25 Boyer JL, Hales MR, Klatskin G. "Idiopathic" portal hypertension due to occlusion of intrahepatic portal veinsby organized thrombi. A study based on postmortem vinylite-injection corrosionand dissection of the intrahepatic vasculature in 4 cases. *Medicine (Baltimore)* 1974;53:77-91
26 Boyer JL, Sen Gupta KP, Biswas SK, Pal NC, Basu Mallick KC, Iber FL, Basu AK. Idiopathic portal hypertension. Comparison with the portal hypertension of cirrhosis and extrahepatic portal vein obstruction. *Ann Intern Med* 1967;66:41-68
27 Nakanuma Y, Tsuneyama K, Ohbu M, Katayanagi K. Pathology and pathogenesis of idiopathic portal hypertension with an emphasis onthe liver. *Pathol Res Pract* 2001;197:65-76
28 Inagaki H, Nonami T, Kawagoe T, Miwa T, Hosono J, Kurokawa T, Harada A, Nakao A,Takagi H, Suzuki H, Sakamoto J. Idiopathic portal hypertension associated with systemic lupus erythematosus. *J Gastroenterol* 2000;35:235-239
29 Watanabe Y, Mizukami T, Egawa T, Okamoto S, Sakauchi M, Takita T, Suzuki N, Sakuma M. A case of progressive systemic sclerosis complicated by idiopathic portalhypertension with severe anemia. *Ryumachi* 1999;39:586-590
30 Sasaki H, Joh K, Ohtsuka I, Ohta H, Ohhashi T, Hoashi S, Takahashi T, Tokuda T,Koyama K, Isogai Y. Interstitial nephritis associated with glomerulonephritis in a patient with Hashimoto's disease and idiopathic portal hypertension. *Intern Med* 1992;31:641-648
31 Imai Y, Minami Y, Miyoshi S, Kawata S, Saito R, Noda S, Tamura S, Nishikawa M, Tajima K, Tarui S. Idiopathic portal hypertension associated with Hashimoto's disease: report ofthree cases. *Am J Gastroenterol* 1986;81:791-795
32 Sekiguchi Y, Amano K, Takano Y, Saito K, Itoh I, Tsuzaka K, Abe T, Takeuchi T. Portal and pulmonary hypertension in a patient with MCTD. *Ryumachi* 1999;39:657-663
33 Nakanuma Y, Nonomura A, Hayashi M, Doishita K, Takayanagi N, Uchida T, Obata Y,Noma K, Ikoma J, Yoshikawa K. Pathology of the liver in +ACI-idiopathic portal hypertension+ACI- associated withautoimmune disease. The ministry of health and welfare disorders of portal circulation research committee. *Acta Pathol Jpn* 1989;39:586-592
34 Saito K, Nakanuma Y, Takegoshi K, Ohta G, Obata Y, Okuda K, Kameda H. Non-specific immunological abnormalities and association of autoimmune diseases in idiopathic portal hypertension. A study by questionnaire. *Hepatogastroenterology* 1993;40:163-166
35 Makharia G, Dhiman RK, Chawla YK, Vasistha RK.Non-cirrhotic portal fibrosis in a patient with rheumatoid arthritis. *Indian J Gastroenterol* 2001;20:197-198
36 Hiyoshi T, Hisano N, Akasu F, Yoshitsugu M, Takemura T, Enomoto H. A case of type 1 diabetes mellitus in an elderly patient with a history of idiopathic portal hypertension. *Nihon Rinsho Meneki Gakkai Kaishi* 2003;26:21-27
37 Tsuneyama K, Harada K, Katayanagi K, Watanabe K, Kurumaya H, Minato H, Nakanuma Y. Overlap of idiopathic portal hypertension and scleroderma: report of two autopsycases and a review of literature. *J Gastroenterol Hepatol* 2002;17:217-223
38 Tokushige K, Komatsu T, Ohzu K, Yamauchi K, Obata H. A defective autologous mixed lymphocyte reaction in patients with idiopathicportal hypertension. *J Gastroenterol Hepatol* 1992;7:270-273
39 Tokushige K, Hirose S, Nishimura H, Fujimori M, Yamauchi K, Obata H, Futagawa S, Shirai T. Abnormal T cell activation and skewed T cell receptor V beta repertoire usage inJapanese patients with idiopathic portal hypertension. *Clin Immunol Immunopathol* 1995;75:206-213
40 Kathayat R, Pandey GK, Malhotra V, Omanwar S, Sharma BK, Sarin SK. Rabbit model of non-cirrhotic portal fibrosis with repeated immunosensitization by rabbit splenic extract. *J Gastroenterol Hepatol* 2002;17:1312-1316
41 Tokushige K, Yamauchi K, Komatsu T, Takasaki K, Hayashi N. Predominant T helper 1 cells in patients with idiopathic portal hypertension. *J Gastroenterol Hepatol* 2000;15:1312-1317
42 Yamaguchi N, Tokushige K, Haruta I, Yamauchi K, Hayashi N. Analysis of adhesion molecules in patients with idiopathic portal hypertension. *J Gastroenterol Hepatol* 1999;14:364-369
43 Reynolds TB, Ito S, Iwatsuki S. Measurement of portal pressure and its clinical application. *Am J Med* 1970;49:649-657
44 Bosch J, Mastai R, Kravetz D, Navasa M, Rodes J. Hemodynamic evaluation of the patient with portal hypertension. *Semin Liver Dis* 1986;6:309-317
45 Okuda K, Kono K, Ohnishi K, Kimura K, Omata M, Koen H, Nakajima Y, Musha H, Hirashima T, Takashi M. Clinical study of eighty-six cases of idiopathic portal hypertension andcomparison with cirrhosis with splenomegaly. *Gastroenterology* 1984;86:600-610
46 Moriyasu F, Nishida O, Ban N, Nakamura T, Miura K, Sakai M, Miyake T, Uchino H. Measurement of portal vascular resistance in patients with portal hypertension. *Gastroenterology* 1986;90:710-717
47 Sarin SK, Sethi KK, Nanda R. Measurement and correlation of wedged hepatic, intrahepatic, intrasplenic andintravariceal pressures in patients with cirrhosis of liver and non-cirrhoticportal

fibrosis. *Gut* 1987;28:260-266
48 El Atti EA, Nevens F, Bogaerts K, Verbeke G, Fevery J. Variceal pressure is a strong predictor of variceal haemorrhage in patients withcirrhosis as well as in patients with non-cirrhotic portal hypertension. *Gut* 1999;45:618-621
49 Okuda K, Nakashima T, Okudaira M, Kage M, Aida Y, Omata M, Musha H, Futagawa S,Sugiura M, Kameda H. Anatomical basis of hepatic venographic alterations in idiopathic portalhypertension. *Liver* 1981;1:255-263
50 Nishida T, Hayakawa K, Ogasawara H, Katsuma Y. Interesting RI accumulation in hepatic images with Tc-99m GSA SPECT scintigraphyin idiopathic portal hypertension. *Ann Nucl Med* 2001;15:53-55
51 Waguri N, Suda T, Kamura T, Aoyagi Y. Heterogeneous hepatic enhancement on CT angiography in idiopathic portalhypertension. *Liver* 2002;22:276-280
52 Raval N, Shah N, Vani SN. Tropical splenomegaly syndrome. *Indian J Pediatr* 1991;58:679-681
53 De BK, Majumdar D, Das D, Biswas PK, Mandal SK, Ray S, Bandopadhyay K, Das TK, Dasgupta S, Guru S. Cardiac dysfunction in portal hypertension among patients with cirrhosis andnon-cirrhotic portal fibrosis. *J Hepatol* 2003;39:315-319
54 Kaymakoglu S, Kahraman T, Kudat H, Demir K, Cakaloglu Y, Adalet I, Dincer D,Besisik F, Boztas G, Sozen AB, Mungan Z, Okten A. Hepatopulmonary syndrome in noncirrhotic portal hypertensive patients. *Dig Dis Sci* 2003;48:556-560
55 Anand AC, Mukherjee D, Rao KS, Seth AK. Hepatopulmonary syndrome: prevalence and clinical profile. *Indian J Gastroenterol* 2001;20:24-27
56 Obama R, Tachikawa H, Yoshii F, Takeoka T, Shinohara Y.A case of idiopathic portal hypertension (IPH) with hypermanganemia presentingas spastic gait. *Rinsho Shinkeigaku* 2002;42:885-888
57 Vassia M, Curciarello JO, Corrons F, Viola M, Zamboni E, Castagno M, JmelnitzkyAC. Idiopathic portal hypertension with splenic infarct. An unreported complication. *Acta Gastroenterol Latinoam* 2001;31:27-30
58 Dumortier J, Bizollon T, Scoazec JY, Chevallier M, Bancel B, Berger F, Ducerf C,Claudel-Bonvoisin S, Paliard P, Boillot O, Trepo C. Orthotopic liver transplantation for idiopathic portal hypertension: indicationsand outcome. *Scand J Gastroenterol* 2001;36:417-422
59 Sarin SK, Govil A, Jain AK, Guptan RC, Issar SK, Jain M, Murthy NS. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. *J Hepatol* 1997;26:826-832
60 Kochhar R, Goenka MK, Mehta SK. Outcome of injection sclerotherapy using absolute alcohol in patients withcirrhosis, non-cirrhotic portal fibrosis, and extrahepatic portal venousobstruction. *Gastrointest Endosc* 1991;37:460-464
61 Sarin SK, Nanda R, Kumar N, Vij JC, Anand BS. Repeated endoscopic sclerotherapy for active variceal bleeding. *Ann Surg* 1985;202:708-711
62 Warren WD, Henderson JM, Millikan WJ, Galambos JT, Bryan FC. Management of variceal bleeding in patients with noncirrhotic portal veinthrombosis. *Ann Surg* 1988;207:623-634
63 Mathur SK, Shah SR, Nagral SS, Soonawala ZF. Transabdominal extensive esophagogastric devascularization with gastroesophagealstapling for management of noncirrhotic portal hypertension: long-term results. *World J Surg* 1999;23:1168-1174
64 Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS. Comparison of endoscopic ligation and propranolol for the primary prevention ofvariceal bleeding. *N Engl J Med* 1999;340:988-993
65 Hirota S, Ichikawa S, Matsumoto S, Motohara T, Fukuda T, Yoshikawa T. Interventional radiologic treatment for idiopathic portal hypertension. *Cardiovasc Intervent Radiol* 1999;22:311-314
66 Romano M, Giojelli A, Capuano G, Pomponi D, Salvatore M. Partial splenic embolization in patients with idiopathic portal hypertension. *Eur J Radiol* 2004;49:268-273
67 Mitra SK, Rao KL, Narasimhan KL, Dilawari JB, Batra YK, Chawla Y, Thapa BR, NagiB, Walia BN. Side-to-side lienorenal shunt without splenectomy in noncirrhotic portalhypertension in children. *J Pediatr Surg* 1993;28:398-401
68 Lytkin MI, Zubarev PN, Kalashnikov SA. Idiopathic portal hypertension. *Vestn Khir Im I I Grek* 2001;160:101-105
69 Soma J, Saito T, Sato H, Ootaka T, Abe K.Membranoproliferative glomerulonephritis induced by portosystemic shunt surgeryfor non-cirrhotic portal hypertension. *Clin Nephrol* 1997;48:274-281
70 Ohta M, Shimada T, Matsufuji H, Yukizane T, Yamada H, Sugimachi K. Surgical treatment of a patient with idiopathic portal hypertension and hepaticencephalopathy. *Hepatogastroenterology* 2001;48:1461-1463
71 Okuda K. Non-cirrhotic portal hypertension versus idiopathic portal hypertension. *J Gastroenterol Hepatol* 2002;17(Suppl 3):S204-S213
72 Sharma D, Agrawal S, Saxena A, Raina VK. A modified technique of devascularization for surgical management of portalhypertension in children. *Trop Doct* 2001;31:93-95
73 Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-termfollow-up study in 568 portal hypertension patients. *Hepatology* 1992;16:1343-1349
74 Sarin SK, Jain AK, Lamba GS, Gupta R, Chowdhary A. Isolated gastric varices: prevalence, clinical relevance and natural history. *Dig Surg* 2003;20:42-47
75 Sarin SK, Jain AK, Jain M, Gupta R. A randomized controlled trial of cyanoacrylate versus alcohol injection inpatients with isolated fundic varices. *Am J Gastroenterol* 2002;97:1010-1015
76 Aggarwal N, Sawhney H, Vasishta K, Dhiman RK, Chawla Y. Non-cirrhotic portal hypertension in pregnancy. *Int J Gynaecol Obstet* 2001;72:1-7
77 Potzi R, Ferenci P, Gangl A. Endoscopic sclerotherapy of esophageal varices during pregnancy-case report. *Z Gastroenterol* 1991;29:246-247