Gallbladder and Pancreas in Henoch-Schönlein Purpura: Review of the Literature

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ABSTRACT

Objective: Involvement of the pancreato-biliary system has been occasionally noted in Henoch-Schönlein purpura. Furthermore, cases of this vasculitis syndrome sometimes develop in the context of a viral hepatitis or after hepatitis vaccination.

Methods: We completed a review of the literature.

Results: Fifty reports published between 1977 and 2015 were retained for the analysis. A pancreato-biliary involvement was recognized in 34 individually well-described patients ($\mathcal{J}: \mathcal{Q} = 19:15$) with severe abdominal pain: pancreatitis (N = 20), acalculous cholecystitis (N = 11), both pancreatitis and cholecystitis (N = 3). In all of the pancreatitis patients, full recovery occurred (within ≤ 3 weeks in three-fourths of the patients). Cholecystectomy was performed in 8 cholecystitis patients. Seventeen Henoch-Schönlein patients ($\mathcal{J}:\mathcal{Q} = 9:8$) were associated with a viral liver disease and 4 ($\mathcal{J}:\mathcal{Q} = 1:3$) with a hepatitis vaccination. The vasculitis syndrome rapidly remitted in the 7 patients accompanying hepatitis A or E, in 2 patients of hepatitis B, and in the 4 patients preceded by a vaccination. Henoch-Schönlein purpura seemed to be serious in 5 patients with chronic hepatitis B and in 3 with chronic hepatitis C.

Conclusions: This analysis indicates that pancreato-biliary involvement is unusual in Henoch-Schönlein purpura. This complication deserves consideration in patients with especially severe abdominal pain. Finally, viral hepatitides and hepatitis vaccinations seem to be rare triggers of Henoch-Schönlein purpura.

Key Words: acalculous cholecystitis, Henoch-Schönlein purpura, hepatitis, kidney disease, pancreatitis, vaccination

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enoch-Schönlein purpura, also known as immunoglobulin A leukocytoclastic vasculitis, is usually triggered by an infectious disease or, more rarely, a vaccination (1). This condition characteristically presents with palpable purpura concentrated in dependent areas, arthralgia or arthritis, abdominal pain, and kidney disease (1).

Copyright © 2016 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition DOI: 10.1097/MPG.00000000000955 What Is Known

- Case reports document the involvement of biliopancreatic system in Henoch-Schönlein purpura.
- Henoch-Schönlein purpura occasionally develops in the context of viral hepatitides.

What Is New

- Bilio-pancreatic involvement is benign and self-remittent in ≈3/4 of Henoch-Schönlein patients. Subjects with bilio-pancreatic involvement are older (5–55 years) than those (3–15 years) without.
- Viral hepatitides may be rare triggers of Henoch-Schönlein purpura. In these patients, prognosis of Henoch-Schönlein purpura is determined by the severity of the underlying liver disease.

Pancreatitis and acalculous cholecystitis are unusual but recognized complications of abdominal vasculitides. Unsurprisingly, therefore, involvement of the pancreato-biliary system has been occasionally noted in Henoch-Schönlein purpura. Moreover, cases of this vasculitis sometimes develop either in the context of an acute or chronic viral liver disease or after hepatitis A or B vaccination. Because textbooks and reviews only marginally mention these associations, we reviewed and analyzed the available literature.

METHODS

Between February and May 2015, we performed a computer-based search with no date limits of the terms (Henoch OR Schönlein OR Henoch-Schönlein OR Schönlein-Henoch OR anaphylactoid purpura OR rheumatoid purpura OR rheumatoid angiitis OR vasculitis) AND (liver OR hepatic OR biliary OR pancreatic OR hepatitis OR vaccination) in the search engine PubMed. In addition, we used our personal files and the bibliography of each identified study. We applied the principles established by the Economic and Social Research Council guidance on the conduct of narrative synthesis and on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (2). For the final analysis, we selected peer-reviewed reports published as full-length article or letter, which include Henoch-Schönlein patients with pancreas, gallbladder, or liver involvement. Cases of this vasculitis syndrome associated with a viral liver disease or preceded by a vaccination against hepatitis A or B infection were also selected. We exclusively retained well-documented original cases presenting subjects of both

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sexes and all ages irrespective of follow-up duration, which had been published in Dutch, English, French, German, Italian, Portuguese, or Spanish. When >1 article reported on the same patient, only the more comprehensive article was included and referenced.

The diagnosis of Henoch-Schönlein purpura, pancreatitis, and cholecystitis established in the original publications, which were often supported by figures depicting skin lesions and imaging studies, was reviewed using recognized criteria. The diagnosis of Henoch-Schönlein purpura was based on the European League Against Rheumatism/Paediatric Rheumatology International Trials Organization/Paediatric Rheumatology European Society criteria (3). The latter include palpable purpura together with at least 1 of the following findings: abdominal pain, leukocytoclastic vasculitis with immunoglobulin A (IgA) deposits, acute arthritis, or arthralgia in any joint and renal involvement as evidenced by pathological urinalysis, with or without a biopsy disclosing mesangial IgA deposits (3). The diagnosis of pancreatitis was made in patients with abdominal pain and amylase or lipase level at least twice the upper limit of normal in the absence of alcohol abuse, gallstones, or prescription of drugs implicated as causing pancreatitis (4). The diagnosis of acalculous cholecystitis was made in patients with right upper quadrant abdominal pain and imaging studies disclosing a significant (\geq 4 mm) gallbladder wall thickening (with or without fluid collection around the gallbladder) in the absence of alternative diagnoses such as calculous cholecystitis (5). The diagnosis of hepatitis A, B, or C was made using standard laboratory techniques. Henoch-Schönlein cases associated with infectious mononucleosis, primary biliary cirrhosis or alcohol abuse, as well as with documented causes of pancreatitis or cholecystitis, were excluded.

From each report dealing with Henoch-Schönlein purpura and pancreato-biliary involvement or viral liver disease or vaccination, we excerpted data on sex, age, presence of abdominal pain preceding the purpura, aminotransferase levels, kidney disease, course, and management. The data were extracted by 2 investigators (R.H. and S.A.G.L.) independently and a consensus was reached on all items. Disagreements were resolved through discussion or adjudicated by a third author (G.P.M.).

The kidney disease was classified as absent in patients with normal urinalysis, mild in patients with hematuria and urine protein/ creatinine ratio <200 g/mol, moderate in patients with hematuria and protein/creatinine ratio >200 g/mol, and severe in patients with protein/creatinine ratio >200 g/mol, hypoalbuminemia (<25 g/L), and pitting edema (6).

Results are given either as frequency or as median and interquartile range. The Fisher exact test was used to compare dichotomous variables and the Mann-Whitney-Wilcoxon rank-sum test to compare continuous variables. Statistical significance was assigned at P < 0.05.

RESULTS

Search Results

A total of 50 peer-reviewed scientific reports (7-57) published between 1977 and 2015 in English (N=41), French (N=4), German (N=2), Spanish (N=2), and Italian (N=1) were retained for the final analysis (Fig. 1). They had been reported from the following continents: Asia (N=22), Europe (N=16), North America (N=8), Africa (N=3), and Australia (N=1). The reports included 34 well-documented Henoch-

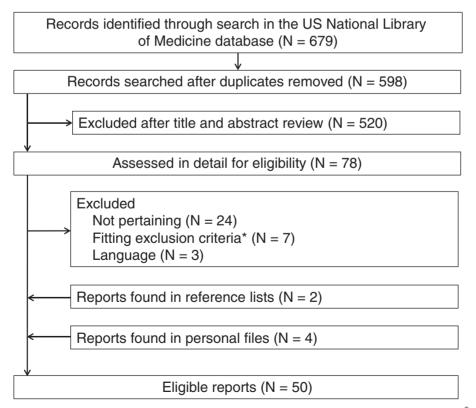


FIGURE 1. Pancreas, gallbladder, and liver in Henoch-Schönlein purpura. Flowchart of the literature search process. *Cases associated with infectious mononucleosis (N=1), primary biliary cirrhosis (N=1), or alcohol abuse (N=2); same case reported in >1 article (N=2); poorly described patients (N=1).

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	All	Pancreatitis	Cholecystitis	Pancreatitis + cholecystitis
N	34	20	11	3
Age, y	15 (7-43)	17 (8-47)	8 (5-35)	6, 8, 30 [*]
Sex, ♂:♀	19: 15	11: 9	6: 5	2: 1
Abdominal pain precedes purpura, N (%)	14 (41)	11 (55)	2 (18)	1 (33)
Aminotransferases elevated, N (%)	11 (32)	5 (25)	4 (36)	2 (67)
Kidney disease, N (%)	17 (50)	10 (50)	5 (45)	2 (67)
Mild	8	3	4	1
Moderate	3	3	0	0
Severe	6	4	1	1

Results are given as either frequency or median and interquartile range (7-38). * Individual values.

Schönlein cases associated with pancreato-biliary involvement (7-38), 17 patients associated with a viral liver disease (39-52) and 4 preceded (53-56) by a hepatitis vaccination. Using the aforementioned inclusion criteria, we always confirmed the diagnosis of Henoch-Schönlein purpura, pancreatitis, or cholecystitis established in the original publications.

Pancreato-Biliary Involvement

Pancreatitis (7–25) was recognized in 20, acalculous cholecystitis (26–35) in 11, and both pancreatitis and cholecystitis (36–38) in 3 individually well-described patients. A kidney disease was noted in 17 of the 34 patients (Table 1). Patients with kidney involvement were significantly older by 21 years than those without (28 [16–52] vs 7 [5–12] years, P < 0.01). Abdominal pain, which was associated with arthralgia or arthritis in 8 patients, preceded the appearance of purpura by ≤ 2 weeks in 14 of the 34 Henoch-Schönlein patients with pancreato-biliary involvement.

Pancreatitis

In addition to the increased amylase or lipase tests, the pancreas appeared diffusely enlarged and hypoechoic on abdominal ultrasound in 8 of the 20 pancreatitis patients. Peripancreatic fluid and bowel wall thickening were noted in 7 and in 5 patients, respectively. Finally, cardiac failure (19) and acute respiratory distress syndrome (11) were observed in each 1 patient. Symptomatic and supportive management was provided in all patients. Steroids were given in 7 patients. In all of the patients, full recovery occurred (within ≤ 3 weeks in 3/4 of the patients). It is true, however, that in 2 patients the clinical remission was observed 3 to 4 months after the diagnosis.

Cholecystitis

Cholecystectomy (open surgery, N=6; laparoscopic surgery, N=2) was performed in 8 of the 11 patients affected with cholecystitis. The intraoperative diagnosis of gallbladder perforation with biliary peritonitis was made in 1 patient (34). Supplemental bile duct stenosis leading to severe secondary cholestatic liver disease was noted in 1 further patient (31). Finally, cholecystitis was associated with intussusception in 1 patient (35).

Cholecystitis and Pancreatitis

None of the 3 patients with concurrent involvement of gallbladder and pancreas underwent surgery. In 1 of these patients,

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a ureteric obstruction was also observed (36). The bilio-pancreatic involvement resolved after ≤ 10 days in 2 and approximately after 4 months in the patient with ureteric obstruction (steroids had been given in this patient).

BIOPSY STUDIES

A skin biopsy, performed in 12 patients with pancreatitis, in 3 with cholecystitis, and in 2 with both cholecystitis and pancreatitis, showed a leukocytoclastic vasculitis with IgA deposits. A kidney biopsy, performed in 7 patients with pancreatitis, revealed mesangial IgA deposits. Histopathology of gallbladder, performed in 7 patients with 2, revealed a leukocytoclastic vasculitis in 4 patients and the distinctive signs of cholecystitis in the remaining 3 patients.

Henoch-Schönlein Purpura Associated With a Viral Liver Disease or Preceded by Hepatitis Vaccination

The literature included also 17 Henoch-Schönlein cases associated with an acute or chronic viral liver disease (39-52) and 4 preceded (53-56) by a hepatitis vaccination (Table 2).

Henoch-Schönlein purpura spontaneously resolved within ≤ 4 weeks in the 7 cases accompanying hepatitis A or E and in the 4 cases preceded by vaccination against hepatitis A or B. No kidney disease was observed in these 11 patients.

Henoch-Schönlein purpura spontaneously resolved without any kidney disease in 5 of 7 hepatitis B patients. These patients also rapidly and spontaneously recovered from the liver disease. A severe respectively a moderate kidney disease occurred in each 1 of the 2 remaining patients, who were affected with a chronic

TABLE 2. Cases of Henoch-Schönlein syndrome associated (40–57)
with a viral liver disease (N $=$ 17) or preceded by hepatitis A or B
vaccination (N = 4)

Trigger	Ν	Age^*	Sex (♂: ♀)
Viral liver disease			
Hepatitis B	7	3.0, 6, 8, 13, 23, 32, 40	2: 5
Hepatitis A	6	2.7, 8, 10, 10, 11, 13	4: 2
Hepatitis C	3	50, 63, 56	3: 0
Hepatitis E	1	6	0:1
Vaccination			
Hepatitis A	2	1.6, 24	1:1
Hepatitis B	2	21, 28	0:2

* Individual values.

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hepatitis B (no follow-up information is available for these patients).

In the 3 patients with chronic hepatitis C (2 of them complicated by liver cirrhosis), Henoch-Schönlein purpura presented in each 1 patient without, with mild or with moderate kidney disease. The long-term prognosis was predicted by the underlying liver disease.

DISCUSSION

The present review indicates that in Henoch-Schönlein purpura there is rarely a clinically relevant pancreato-biliary involvement. Furthermore, this condition is sometimes triggered by a viral liver disease or preceded by a vaccination against hepatitis A or B.

It is assumed that the prognosis of Henoch-Schönlein purpura is essentially determined by the severity of the accompanying kidney disease (1,6). This impression is supported by the present analysis: in $\approx 3/4$ of the Henoch-Schönlein patients with pancreatobiliary involvement the disease was benign and self-remittent.

Ninety percent of Henoch-Schönlein cases occur between the ages of 3 and 15 years (1), cases with pancreato-biliary involvement between the ages of 5 and 55 years. Recommended management of pancreatitis includes proper fluid management, pain relief, and nutritional support (4), that of acalculous cholecystitis surgery and antibiotics (5). We speculate that steroids as well deserve consideration in cholecystitis or pancreatitis that develops in the context of a vasculitis syndrome. All the more so because in Henoch-Schönlein purpura steroids effectively treat abdominal pain, which mostly results from bowel wall swelling and bleeding.

In a retrospective case series from the Republic of China including 225 apparently unselected children with Henoch-Schönlein (57), imaging studies disclosed abnormalities of the biliary system in 14 (6%) of them: gallbladder wall thickening $\geq 4 \text{ mm} (N=7)$, sludge (N=5), gallbladder dilatation (N=1), and bile duct dilatation (N=1). These data, which deserve further confirmation, point to the possible existence, in some Henoch-Schönlein patients, of gallbladder abnormalities that may predispose to acalculous cholecystitis.

Henoch-Schönlein cases often develop after an upper respiratory infection (1). Further infectious triggers include Epstein-Barr virus, Helicobacter, Legionella, Mycoplasma, Parvovirus, Varicella zoster virus, or Yersinia (1). Cases also have been reported following vaccination (1). The present analysis indicates that viral hepatitides and vaccination against hepatitis A or B may be further possible triggers of this vasculitis. The number of reported Henoch-Schönlein patients temporally associated with viral hepatitides or vaccination against hepatitis is limited. It is true, however, that most vasculitides associated with hepatitides or vaccininations are "non-Henoch-Schönlein vasculitides" (58). Henoch-Schönlein purpura that develops after vaccination against hepatitis or in the context of hepatitides, which usually rapidly resolve on their own, is benign and remits soon. On the contrary, cases that develop in the context of chronic hepatitis B and C may be serious. In the latter patients, the long-term prognosis is essentially determined by the severity of the underlying liver disease

Some limitations of this work should be mentioned. First, it results from the small number of reported patients, often without or with a brief follow-up. Second, diagnostic and therapeutic recommendations arise from authors' opinions. Third, data on liver involvement in patients not triggered by a viral liver disease are inconsistent. Fourth, the relation between viral liver diseases respectively vaccinations against hepatitis A or B and Henoch-Schönlein purpura is so far undemonstrated. In conclusion, this analysis indicates that pancreato-biliary involvement is unusual in this vasculitis. This complication deserves consideration in patients with especially severe abdominal pain. Testing for lipase and ultrasonic imaging by an examiner aware of the diagnostic suspicion represents, in our opinion, the most reliable diagnostic tools currently available for Henoch-Schönlein patients with suspected pancreato-biliary involvement. Finally, the present analysis demonstrates that viral liver disease and, to a lesser extent, hepatitis vaccinations may be rare triggers of Henoch-Schönlein purpura.

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