นิพนธ์ต้นฉบับ

Chronic hepatitis : A clinico-pathologic study

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การศึกษาร่วมทางคลินิค และพยาธิวิทยา ในผู้ป่วยโรคตับอักเสบเรื้อรังจำนวน 50 ราย โดยเปรียบเทียบลักษณะทางคลินิค ชีวเคมี ภูมิคุ้มกัน และพยาธิสภาพระหว่างผู้ป่วย chronic persistent hepatitis 12 ราย, chronic active hepatitis ชนิดที่มีความรุนแรงปานกลาง 18 ราย, และชนิดที่มีความรุนแรงมาก ซึ่งมักร่วมกับตับแข็ง 20 ราย พบว่าส่วนใหญ่ของผู้ป่วยทั้ง 3 กลุ่มเป็นชายและร้อยละ 74 ของผู้ป่วยปรากฏมี HBsAg ในซีรั่ม ในกลุ่มผู้ป่วย chronic active hapatitis ระยะเวลาของตับอักเสบในผู้ป่วยที่ปรากฏมี HBsAg ในซีรั่มจะยาวนานกว่าในผู้ป่วยที่ไม่ปรากฏมี HBsAg ในซีรั่มอย่างมีนัยสำคัญทางสถิติ ($p < .05$) และผู้ป่วยที่ไม่แสดงอาการมักพบในกลุ่มที่ปรากฏมี HBsAg ในซีรั่ม ($p < .05$)

จากการศึกษาทางพยาธิวิทยาพบว่า piecemeal necrosis, portal fibrosis ร่วมกับ fibrous bridging, ภาวะตับแข็งและน้ำดีคั่ง พบในกลุ่มของผู้ป่วย chronic active hepatitis ได้บ่อยกว่า กลุ่มผู้ป่วย chronic persistent hepatitis ความแตกต่างทางพยาธิสภาพนี้มีส่วนช่วยในการวินิจฉัยแยกระหว่าง chronic persistent hepatitis กับ chronic active hepatitis

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The histological classification of chronic hepatitis introduced in 1968 by De Groote et al[1] and slightly modified in 1977 by the international group[2] is still widely used. The Thai liver study group also published histopathological classification of liver disease as based on Fogarty International Center Recommendation in 1976.[3] They classified chronic hepatitis into chronic persistent (CPH) and chronic aggressive or chronic active hepatitis (CAH) of moderate and severe activity. Chronic persistent hepatitis, the more benign form, was characterized by mild inflammation mainly confined to portal tract with or without superimposed features of acute hepatitis in the liver parenchyma. The other form of chronic hepatitis, chronic active hepatitis, was characterized by more extensive inflammation in the portal tract and liver parenchyma. Piecemeal necrosis (periportal necrosis) is usually demonstrated. Chronic active hepatitis usually progresses to cirrhosis and even liver cell carcinoma.

Although chronic hepatitis is one of the major health problems in Thailand, available data from clinical studies are scarce.[4, 5] The aim of this clinicopathological study was to 1) correlate clinical and laboratory features with histological severity of chronic hepatitis. 2) Compare the clinical feature of HBsAg positive and negative chronic active hepatitis.

Materials and Method

Patients admitted to Chulalongkorn hospital during 1974 to 1978, who had liver biopsy findings diagnostic of chronic hepatitis were selected for the study. These patients presented with clinical evidence of liver disease such as jaundice, hepatomegaly, abnormal liver function tests or positive Hepatitis B surface antigen (HBsAg) for a duration of at least 6 months before biopsy. Patients who had less then 6 months history of liver disease were also accepted if clinical or histological evidence of cirrhosis was present. Fifty patients were finally selected, none had been exposed to known hepatotoxic drugs or heavy alcoholic intake (consuming more than 80 grams ethanol daily). Two patients had hepatitis after blood transfusion.

All biopsies except one were needle biopsies. Liver tissue was fixed in neutral formalin and stained by standard methods including hematoxylin and eosin, silver impregnation for reticulin fibers and Masson's Trichrome stain. Shikata's orcein stain for detection of HBsAg was also performed.[6, 7] All liver biopsies were interpreted blindly by one of us (P.S.). Attempt was made to classify the histologic lesions into 3 groups (CPH, CAH with moderate, activity and CAH with severe activity) according to the criteria proposed by the international liver group.

Chronic persistent hepatitis : chronic inflammatory infiltation, mostly portal, with preserved lobular architecture and little or no fibrosis. Piecemeal necrosis is absent or slight. (Fig 1)

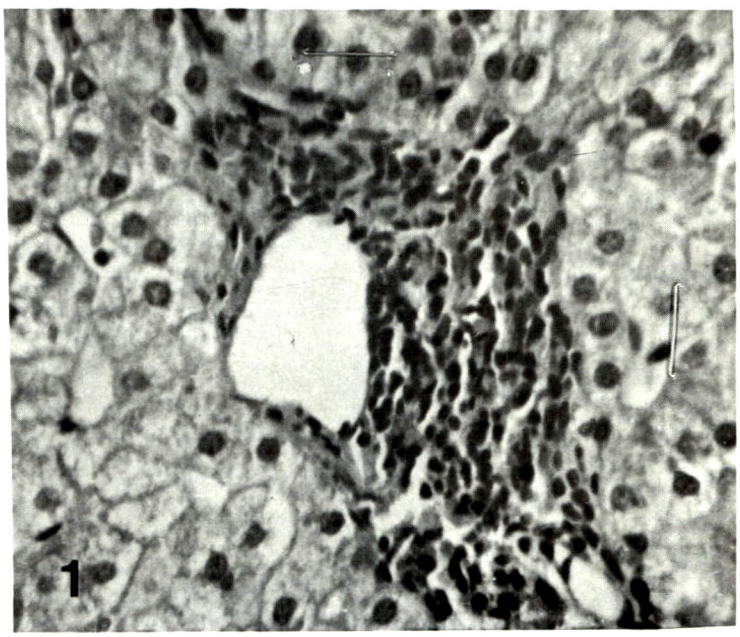

Fig. 1 Chronic persistent hepatitis showing mononuclear cells infiltration in portal tract. There is no periportal inflammation or necrosis. H & E × 400

Chronic active hepatitis with moderate activity : only slight piecemeal necrosis and no overt bridging necrosis. (Fig 2)

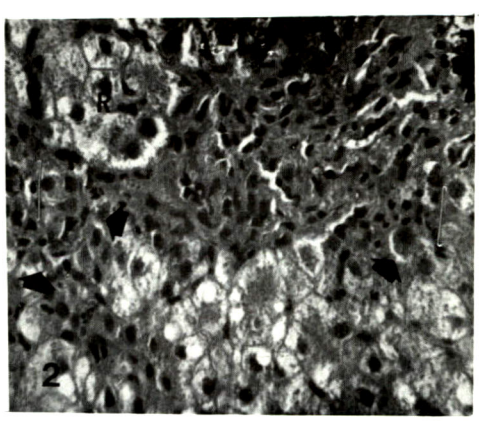

Fig. 2 Chronic active hepatitis, moderate activity showing enlarged portal tract with a pseudorosette (R). Piecemeal necrosis(Arrows) and acidophilic body (Arrow) are also seen. H & E × 400

Chronic active hepatitis with severe activity : Chronic inflammatory infiltration involving portal tracts and extending into the parenchyma, with piecemeal necrosis and formation of intralobular septa. Activity, as shown by piecemeal necrosis and inflammation, is severe. (Fig 3 A, 3 B)

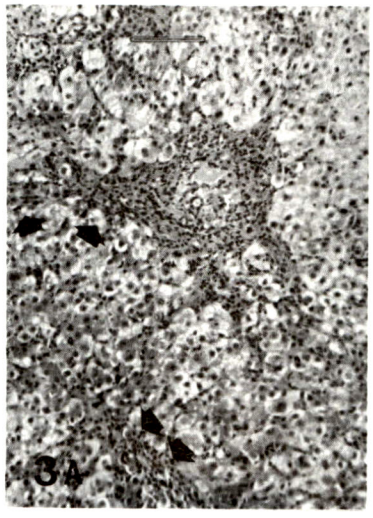

Fig. 3A. Chronic active hepatitis, severe activity showing fibrous bridging fibrosis between portal tracts (Arrows). H & E × 100

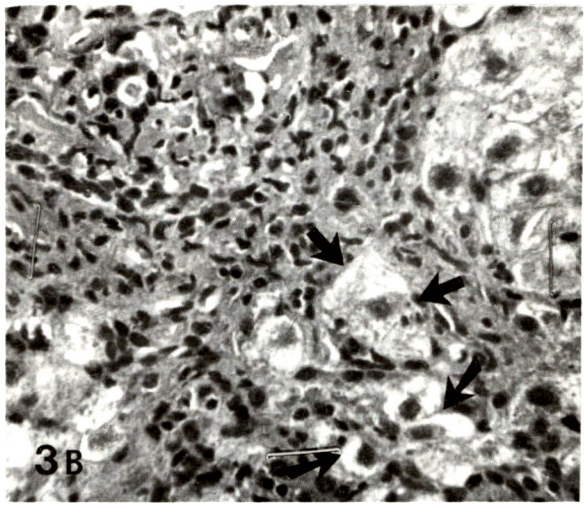

Fig. 3B. Chronic active hepatitis, severe activity showing portal and periportal inflammation with trapped hepatocytes (Arrows). H & E × 400

Serum hepatitis B surface antigen (HBsAg) in the patients was determined by counter – immuno – electrophoresis. Biochemical study of serum proteins (albumin, globulin and gamma-globulin), liver function tests (bilirubin, alkaline phosphatase, SGPT, prothrombin time) and immunoserological study (antinuclear antibody, smooth muscle antibody and anti-mitochondria antibody) were done by the hospital clinical laboratory as previously described.[8]

Result

Histological features

As shown in Table 1, 12 patients had histological diagnosis of CPH, and 38 patients had CAH (18 with moderate activity, 8 with severe activity and 12 with cirrhosis). Positive orcein staining for HBsAg was found in only 14 percent, while serum HBsAg was positive in 74 percent of the cases.

As shown in Table 2 periportal inflammation accompanied by portal fibrosis with fibrous bridging was more frequently seen in chronic active hepatitis compared to chronic persistent hepatitis. Piecemeal necrosis was also more frequently present in chronic active hepatitis of both moderate and severe activity.

Clinical features

The age, sex, duration of hepatitis, serum HBsAg, and the presenting symptoms of the 50 patients were compared according to the severity of histological findings as shown in Table 3. Most patients were male (78 %) and were 20–40 years of age (Mean age = 33 years). Patients with CPH had a lower mean age than the other two groups. There was significant difference in the duration of hepatitis between CPH and CAH patients, this is mainly due to the relatively high number of asymptomatic (carriers of HBsAg in the CPH group 42 %).

Comparison of the clinical features showed that 72 % of the whole group manifested evidence of clinical hepatitis (prolonged acute hepatitis or recurrent hepatitis), which was found more frequently in the group of CAH with severe activity. Twenty-two percent of the whole group were asymptomatic, with the prevalence of 5 % in the group of severe CAH and cirrhosis. Symptoms and signs of decompensated cirrhosis (ascites, edema, and encephalopathy) were found only in the last group. Extrahepatic manifestations eg arthritis, nephritis and pericarditis were not present in any patient.

Laboratory features :

In the biochemical tests of liver function (Table 4), mean serum bilirubin was significantly higher in CAH than in CPH. There was no significant difference between the three groups in the mean level of serum alkaline phosphatase, aminotransferase (SGPT) and albumin. Hyperglobulinemia and hypergammaglobulinemia were more prominent in CAH with severe activity than CAH of moderate activity and CPH. Autoantibodies were present in some patients but only in low titers. Anti-smooth

muscle antibodies (SMA) and anti-mitochondria antibodies (AMA) were positive only in CAH. Anti-nuclear antibodies (ANA) were infrequently found in all groups.

To determine the clinical implications of HBsAg in chronic hepatitis, findings in groups of HBsAg positive and negative CAH were compared (Table 5). HBsAg positive patients showed a prominence of males, younger age and longer duration of hepatitis. HBsAg negative patients had a higher incidence of clinical hepatitis, higher mean serum bilirubin and lower albumin level. No significant difference in immunoserological markers and histological features were found.

Discussion

Chronic hepatitis is diagnosed by the presence of hepatic parenchyma inflammation for a duration of 6 months or longer.[9] Further subdivision or chronic hepatitis into different types is most accurately done according to histopathological features. CPH is characterized by inflammation largely confined to portal tracts, with or without superimposed features of acute hepatitis in the lobule.[10, 11, 12] CAH is defined by the presence of portal and periportal inflammation and piecemeal (periportal) necrosis. CAH may vary from a minimal lesion distinguishable with difficulty from CPH, to one with moderate severity without cirrhosis, and the most severe one with widespread necrosis and inflammation, rosettes formation, bridging hepatic necrosis, nodular regeneration and complete disruption of hapatic architecture.[12,13,14]

From this study as well as other two studies from Thailand, CAH is more common than CPH. Chronic lobular hepatitis (CLH), the third histological category characterised by spotty necrosis and inflammation which were confined to the lobules[14,15,16] was seldom diagnosed and therefore not included in this study.

It has been widely accepted that CPH and CAH have different prognoses and require different therapeutic approach, CPH produces no cumulative damage to the liver,[10,11,12] while CAH produce cumulative liver damage with eventual liver cirrhosis, liver failure and even hepatocellular carcinoma.[13,17,18] Long term follow-up of chronic viral hepatitis by Sucha Kurathong et al[5] however demonstrated that CPH may progress to CAH and cirrhosis.

Chronic hepatitis may be asymptomatic and its presence may be suspected when abnormal physical findings or laboratory tests such as enlargement of the liver or spleen, vascular spiders, abnormal liver function tests or HBsAg are found on routine check up.[1, 2, 12] Others may be symptomatic, and present with fatique, weakness or jaundice. Bleeding esophageal varices, ascites and hepatic encephalopathy are rare presenting features. In this study, 22% of the group

were asymptomatic, 72% presented with clinical evidence of hepatitis and 6% with manifestation of decompensated cirrhosis. Arthralgia as well as other extrahepatic manifestation of presumed autoimmune disorders eg thyroiditis, pericarditis, Coomb's positive hemolytic anemia which have been described in the Western literature, have not been found.

The most significant biochemical indicator of chronic hepatitis is a sustained elevation of the serum aminotransferase level. The level of aminotransferases (SGOT and SCPT) are usually 5 to 10 times that of normal. Hyperglobulinemia especially high gamma globulin which is considered essential in the diagnosis of CAH in the literature[19] was not usually found in our cases. Non specific autoantibodies (anti-smooth mucle, anti-nuclear and anti-mitochondria) were found in about one third of patients, but only in low titers.

Biochemical tests may indicate severity of the disease since evidence of impaired overall hepatocellular function is more indicative of significant hepatocellular damage and therefore of CAH rather than CPH. These parameters include a low serum albumin level, a high serum globulin especially gamma globulin, an elevated serum bilirubin, and low prothrombin concentration. From this study, the biochemical tests which showed some difference between CPH and CAH were serum bilirubin, serum globulin and gamma globulin. Other investigators found standard liver chemistry tests not reliably correlate with the severity of the histological lesions,[12, 20] and demonstated that some recently developed tests, such as the aminopyrine breath test[20] and serum bile acids[20, 21, 22] which measure specific liver functions were more useful in predicting the histological severity of chronic hepatitis than were standard liver chemistries.

Report from many countries have domonstrated a close relation between hepatitis B infection and chronic hepatitis. Studies from the United Kingdom[23] Scandinavia,[24] Germany[25] and Australia[26] found a prevalence of hepatitis B Surface antigenemia of 21, 25%, 31% and 26% in CAH and 25%, 48.3%, 46.2% and 47% in CPH respectively. The studies from areas with high HBsAg carrier rates showed a more significant role of hepatitis B infection in the etiology of chronic hepatitis. The frequency of association as high as 90% has been reported from Taiwan.[27] The present study showed that 28/38 (74%) of our patients with CAH and 9/12 (75%) with CPH were HBsAg positive.

Because a more sensitive serologic test for HBsAg such as radioimmunoassay or additional tests for HBV investigation such as anti-HBs and anti-HBc were not available in this study, the prevalence of HBV associated chronic hepatitis may be slightly underestimated. Any how this

finding is consistent with the other 2 studies[4, 5] from Thailand which found that 76% and 88% respectively of their patient with CAH were HBsAg positive. The prevalence of hepatitis B surface antigenemia was 91% in CPH cases reported from Ramathibodi hosptial using compelment fixation test.[5]

Several investigators have compared findings in CAH with and without hepatitis B surface antigen. Differences is sex, age and incidence of non-organ specific immuno-serological markers have been described.[28, 29, 30] Our finding confirmed the predominance of male with HBsAg positive CAH found in previous studies, but not the higher age of patients with HBsAg positive disease. Similarly, the presence of non-organ specific immunoserological markers in high titer in HBsAg negetive patients, was not substantiated. As the incidence of such autoantibodies were present infrequently and in low titers in both groups. HBV-associated CAH is therefore indistinguishable from CAH not associated with HBV by clinical and biochemical features. The presence of ground-glass hepatocytes, positive orcein stain for HBsAg in liver tissue is circumstantial evidence of an HBV etiology. Natural history of HBsAg positive CAH has been incompletely described. Initial observation suggested a slow progression of the untreated disorder in comparison with HBsAg negative CAH.[29] Subsequent studies, however suggested a more aggressive course, with poor response to treatment programmes with prednisone and azathioprine.[30,31,32] About one half to two-thirds of the patients developed cirrhosis within 2-5 years[5, 17], 6 of the 57 patients died within 10 years of diagnosis, and one from hepatocellular carcinoma.[33]

Summary : The clinical, biochemical, immunological and histological features in twelve patients with chronic presistent hepatitis, 18 patients with chronic active hepatitis of moderate activity and 20 patients with chronic active hepatitis of severe activity were compared. Young males were predominated in all 3 groups of the patients, and 74% of patients had positive HBsAg in their sera. Of the 38 patients with chronic active hepatitis, the duration of hepatitis was statistically different between HBsAg positive and HBsAg negative patients ($P < .05$). Asymptomatic patients were found more often in HBsAg positive patients than in the negative ones ($P < .05$)

Histologically, piecemeal necrosis, portal fibrosis with fibrous bridging, cirrhosis and cholestasis were found more frequently in 2 groups of chronic active hepatitis patients than in chronic persistent hepatitis patients. These histological difference would be of help in differentiating between chronic persistent hepatitis and chronic active hepatitis.

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Table 1. Hepatic lesions in 50 patients :

	No (%)
Chronic persistent hepatitis	12 (24%)
Chronic active hepatitis (activity moderate)	18 (36%)
Chronic active hepatitis (activity severe)	8 (16%)
Chronic active hepatitis c̄ cirrhosis	12 (24%)
Orcein stain positive	7 (14%)
Serum HBsAg positive	37 (74%)

Table 2 Hepatic Lesions in Liver Biopsies

	CPH (N=12)	CAH(Mod) (N=18)	CAH (Severe + Cirrhosis) (N=20)
	No. Cases (%)	No. Cases (%)	No. Cases (%)
Inflammation			
Portal	11 (92%)	18 (100%)	20 (100%)
Periportal	0 (0)	18 (100%)*	20 (100%)*
Intralobular	10 (83%)	7 (39%)*	4 (20%)**
Hepatocellular Necrosis			
Focal Necrosis	11 (92%)	7 (39%)*	4 (20%)**
Piecemeal (Periportal)	1 (8%)	14 (78%)**	18 (90%)**
Bridging Necrosis	0 (0%)	0 (0%)	0 (0%)
Fibrosis			
Portal	6 (50%)	8 (44%)	4 (20%)
Portal with fibrous Bridging	0 (0%)	5 (28%)*	15 (75%)*
Cirrhosis	0 (0%)	0 (0%)*	12 (60%)*
Cholestasis	1 (8%)	6 (33%)	10 (50%)*
Acidophilic Body	3 (25%)	5 (28%)	9 (45%)
Orcein Stain Positivity	2 17(%)	1 (5%)	4 (20%)

* = $P < .05$ VS CPH

** = $P < .005$ VS CPH

Compaired test by t-test of proportion.

Table 3 Clinical features

	I CPH (n = 12)	II CAH (Moderate) (n = 18)	III CAH(severe)+cirrhosis (n = 20)
Age, year (mean ± SD)	26.33 ± 9.75	36.83 ± 12.44[a]	43.40 ± 10.77[a]
Sex, male	9 (75%)	12 (67%)	18 (90%)
Duration of hepatitis, months (mean±SD)	18.25 ± 11.30	10.22 ± 13.32[a]	7.90 ± 5.79[a]
Serum $HBsAg^+$	9 (75%)	12 (67%)	16 (80)
Asymptomatic	5 (42%)	5 (28%)	1 (5%)
Clinical hepatitis	7 (58%)	13 (72%)	16 (80%)
– prolonged hepatitis	1 (8%)	9 (50%)	8 (40%)
– recurrent hepatitis	6 (50%)	4 (22%)	8 (40%)
Decompensated cirrhosis	0 (0%)	0 (0%)	3 (15%)[a,b]

a : $p < 0.05$ Vs gr I
b : $p < 0.05$ Vs gr II

Table 4 Biochemical and Immunoserological findings :

	I CPH (n = 12)	II CAH (Moderate) (n = 18)	III CAH (severe)+cirrhosis (n = 20)
Bilirubin (0.1–1.0 mg/dl)	3.41 ± 3.55	12.65 ± 14.41[a]	10.32 ± 10.36[a]
Alkaline phosphatase (9–35 lu)	44.58 ± 21.67	56.27 ± 34.12	52.15 ± 21.01
SGPT (upto 35 KU)	285.33 ± 478.37	471.66 ± 558.20	302.36 ± 353.73
Albumin (4.3–5.7 gm/dl)	4.0 ± 0.81	3.45 ± 1.06	3.21 ± 0.79
Globulin (1.2–3.5 gm/dl)	3.30 ± 0.85	3.77 ± 1.08	3.94 – 0.94[a,b]
γ–Globulin (1.5–1.8 gm/dl)	1.76 ± 0.28	2.22 ± 0.54	2.48 ± 0.76[a,b]
Prothrombin time (80–100% control)	95.90 ± 0.28	94.00 ± 6.27	86.15 ± 11.47[a,b]
ANA (> 1 : 10)	3/9 (33%)	21/4 (14%)	4/16 (25%)
SMA (> 1 : 10)	0/9 (0%)	2/14 (14%)[a]	2/16 (13%)[a]
AMA (> 1 : 10)	0/9 (0%)	2/14 (14%)[a]	1/16 (6%)[a]

a : $p < 0.05$ Vs gr I
b : $p < 0.05$ Vs gr II

Table 5 Contrasting features between HBsAg+ and HBsAg⁻ CAH

	HBsAg$^+$ CAH (n = 28)	HBsAg$^-$ CAH (n = 10)	Student's t-test
Clinical feature			
Sex, Male	26 (93%)	4 (40%)	P < .05
Age, Yr (mean ± SD)	33.92 ± 11.80	40.10 ± 9.72	NS
Duration of hepatitis, month (mean ± SD)	10.89 ± 10.32	3.70 ± 1.15	P < .05
Asymptomatic	7 (25%)	0 (0%)	P < .05
Clinical hepatitis	19 (68%)	9 (90%)	NS
Decompensated cirrhosis	2 (7%)	1 (10%)	NS
Biochemical features			
Bilirubin, mg/dl (Mean ± SD)	9.20 ± 11.43	14.84 ± 12.17	NS
AP, Iμ (Mean ± SD)	57.46 ± 24.48	71.60 ± 41.18	NS
SGPT. Kμ (Mean ± SD)	352.30 ± 447.64	343.80 ± 258.64	NS
Albumin, g/dl (Mean ± SD)	3.41 ± 0.86	3.28 ± 0.64	NS
Globulin, g/dl (Mead ± SD)	3.98 ± 09.3	3.71 < 1.11	NS
γ-globulin, g/dl (Mean ± SD)	2.56 > 0.63	2.17 > 0.63	NS
Immunoserological feature			
ANA pos (> 1 : 10)	4/22 (18%)	2/8 (25%)	NS
SMA pos (> 1 : 10)	3/22 (14%)	1/8 (13%)	NS
AMA pos (> 1 : 10)	1/22 (5%)	2/8 (25%)	NS
Histological features			
CAH (Moderate)	12 (43%)	6 (60%)	NS
CAH (Severe)	6 (21%)	1 (10%)	NS
CAH + Cirrhosis	10 (36%)	3 (30%)	NS

( ) : percent, NS : not significant

อ้างอิง

1. De Groote J, Desmet VJ, Gedigk P, Korb G, Popper H, Poulsen H, Scheuer PJ. A classification of chronic hepatitis. Lancet 1968 Sep 14; 2 (7568) : 626-628
2. Bianchi L, De Groote J, Desmet VJ, Gedigk P, Korb G, Popper H, Poulsen H. Acute and chronic hepatitis revisited : reviews by an international group. Lancet 1977 Oct 29; 2 (8044) : 914-919
3. Thai liver study group. Current histopathological classification of liver disease as based on Fogorty International Center recommendation, 1976. Thai Med J 1978; 2 : 291-300

4. Chainuvati T, Viranuvatti V. Chronic active hepatitis in Thailand (abstract). Meeting. Gastoenterology Association of Thailand, Bangkok, August 9, 1979, p. 9
5. Kurathong S, Puyagnpta S, Akrawongse K, Lerdverasirikul P, Bunyaratavej S. Chronic Viral hepatitis : A Study of 35 patients followed during 1970-1979. Ramathibodi Med J 1982 ; 5 : 233-244
6. Shikata T, Uzawa T, Yoskiwara N. Staining methods of Australia antigen in paraffin section-detection of cytoplasmic inclusion bodies. Jap J Exp Med 1974 Feb ; 44 (2) : 25-36
7. Suwangool P. Orcein staining for detetion of Australia antigen (HBsAg) in paraffin sections of liver biopsy. Chula Med J 1979 ; 23 (Suppl) : 24-32
8. Israsena S, Seriburi O, Sakulramrung R, Vejjajiva S. Hepatitis B surface antigen and antoantibodies in chronic liver diseases. Chula Res J 1981 Jun ; 8 : 67-75
9. Nomenclature, Diagnostic criteria, and Diagnostic Methodology for Diseases of the liver and Biliary Tract. Fogarty International Proc., No. 22. U.S. Government Printing office. 1976, pp 1-11
10. Dietrichson O. Chronic persistent hepatitis : a clinical, serological and prognostic study. Scand J gastroentol 1975 ; 10 (3) : 249-255
11. Becker MD, Scheuer PJ Baptista A, Sherlock S. Prognosis of chronic persistent hepatitis. Lancet 1970 Jan 10 ; 1 (7637) : 53-57
12. Fung WP, Tan KK, Tye CY. Chronic hepatitis-clinicopathological differentiation between active chronic hepatitis and recurrent or persistent (viral) hepatitis. Singapore Med J 1972 Oct ; 13 (5) : 216-223
13. Schalm SW, Korman MG, Summerskill WHJ, Czaja AJ, Baggenstoss AH. Severe chronic active liver disease : Prognostic significance of initial morphologic patterns. Am J Dig Dis 1977 Nov ; 22 (11) : 973-980
14. Scheuer PJ. Liver biopsy in chronic hepatitis 1968-78. Gut 1978 Jun ; 19 (6) : 554--557
15. Popper H, Schaffner F. The vocabulary of chronic hepatitis. N Eng J Med 1971 May 20 ; 284 (20) : 1154-1156
16. Liaw YF, Chu CM, Chen TJ, Wu CS. Chronic labular hepatitis : a clinicopathological and prognostic study. Hepatology 1982 Mar-Apr ; 2 (2) : 258-262
17. De Groote J, Fevery J, Lepoutre L. Long-term follow-up of chronic active hepatitis of moderate severity. Gut 1978 Jun ; 19 (6) : 510-513
18. Okuno T, Okanoue T. Takino T. Prognostic significance of bridging necrosis in chronic active hepatitis. Gastoenterologia Japonica 1983 ; 18 : 577-584
19. Geall MG, Schoenfield LJ, Summerskill WHJ. Classification and treatment of chronic active liver disease. Gastoenterology 1968 Dec ; 55 : (6) 724-729

20. Moroe PS, Baker AL, Schneider JF, Krager PS, Klein PD, Schoeller D. the aminopyrine breath test and serum bile acids reflect histologic severity in chronic hepatitis. Hepatology 1982 May-Jun; 2 (3): 317-322
21. Pennington CR, Ross PE, Bouchier IAD. Serum bile acids in the diagnosis of hepatobiliary disease. Gut 1977 Nov; 18 (11) : 903-908
22. Korman MG, Hofmann AF, Summerskill WHJ. Assessment of activity in chronic active liver disease : serum bile acids compard with conventional tests and histology. N Eng J Med 1974 Jun 20; 290(25): 1399-1402
23. Vischer TL. Australia antigen and autoantibodies in chronic hepatitis. Br Med J 1970 Jun 20; 2: 695-698
24. Dietrichson O. Chronic active hepatitis: aetiological considerations based on clinical and serological studies. Scand J Gastoenterol 1975; 10 (6): 617-624
25. Van Waes L, Segers J, Van Egmond JB, Barbier F, Wieme R, Demeulenaere L. Chronic liver disease and hepatitis-B antigen : a prospective study. Br Med J 1974 Aug 17; 3 (5628): 444-446
26. McCaughan GW, Parsons C, Batey RG, Gallagher ND. The importance of hepatitis B infection in the aetiology of chronic hepatitis: a Sydney Hospital experience. Aust NZ J Med 1982 Feb; 12 (1): 19-21
27. Chen DS, Sung JL. Hepatitis B virus infection and chronic liver disease in Taiwan. Acta hepatogastroenterol (Stuttg) 1978 Dec; 25 (6) : 423-430
28. Bulkley BH, Heizer WD, Goldfinger SE, Isselbacher KJ. Distinctions in chronic active hepatities based on circulating hepatitis-associated antigen. Lancet 1970 Dec 16; 2 (7687): 1323-1326
29. Dudley FS, Schener PJ, Sherlock S. Natural history of hepatitis-associated antigen-positive chronic liver disease. Lancet 1972 Dec 30; 2 (7792): 1388-1393
30. Schalm SW, Summerskill WAL, Gitnick GL, Elveback LR Contrasting features and responses to treatment of severe chronic active liver disease with and without hepatitis Vs antigen. Gut 1976 Oct; 17 (10): 781-786
31. Lam KC, Lai CL, Ng RP, Trepo C, Wu PG. Deleterious effect of prednisolone in HBsAg-positive chronic active hepatitis. N Eng J Med 1981 Feb 12; 304 (7): 380-386
32. Jorge AD, Sanchez C. Therapeutic evaluation of chronic aggressive hepatitis and its relation to the Australian antigen. Acta Hepatogastroenterol (Stuttg) 1978 Jun; 25 (3) : 179-184
33. Isuji T, Naito K, Tokuyama K, Okada T, Takata S, Araki K, Shinohara T, Inoue J, Onoue K. Follow-up ten years after corticosteroid therapy for chronic active hepatitis type B. Hepatogastroenterology 1980 Apr; 27 (2): 85-90

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