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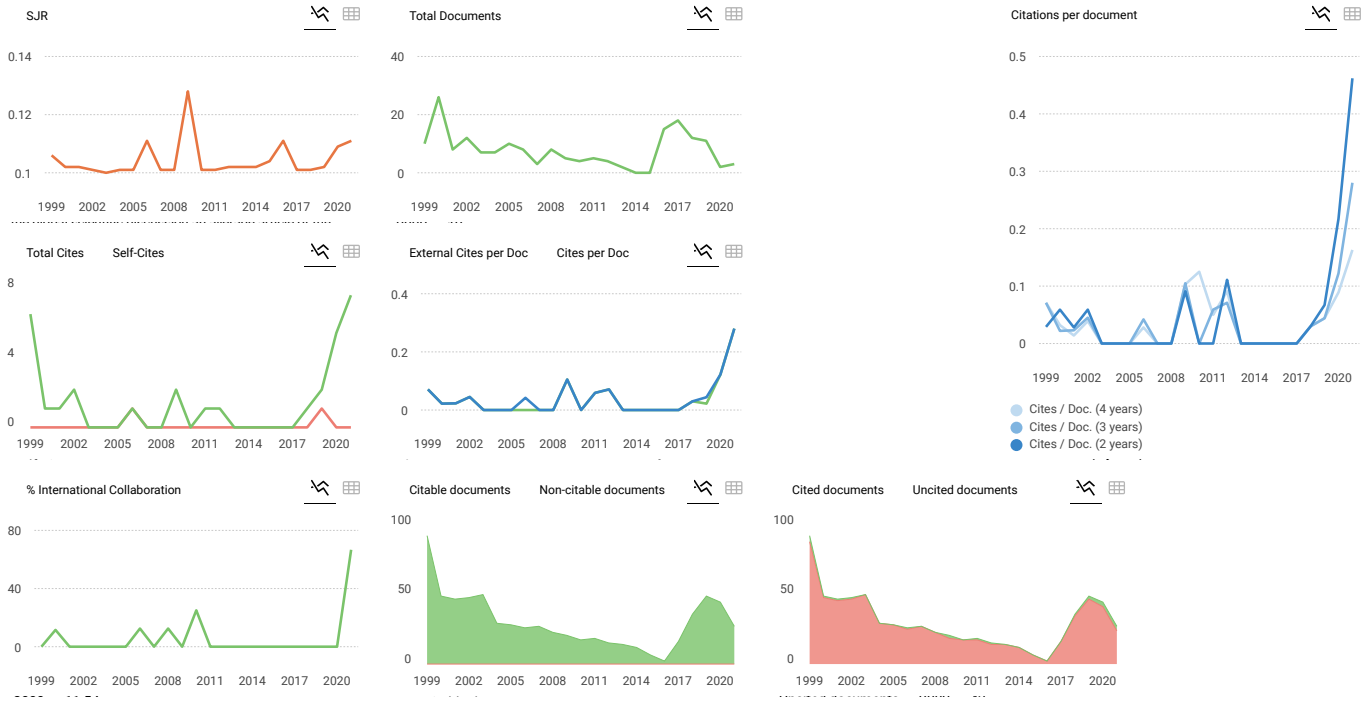

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Title : CORRELATION BETWEEN INTERFERON- γ EXPRESSION, CHOLESTASIS GRADING, AND BILIARY ATRESIA INCIDENCE IN NEONATAL CHOLESTASIS

Author : Bagus Setyoboedi, Ahmad Mahfur, Alphania Rahniayu, Anang Endaryanto, Sjamsul Arief,

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CORRELATION BETWEEN INTERFERON- γ EXPRESSION, CHOLESTASIS GRADING, AND BILIARY ATRESIA INCIDENCE IN NEONATAL CHOLESTASIS

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Abstract— Background: Biliary Atresia (BA) is still a challenge because its pathogenesis remains unclear. It is suggested that interferon gamma (IFN-γ) has important role in its pathogenesis. **Aims:** To analyze correlation between IFN-γ expression, cholestasis grading, and biliary atresia incidence in neonatal cholestasis. **Methods:** It is an analytic observational study within neonatal cholestasis subjects 1-12 months age. Liver biopsies were performed on these subjects. Subjects were divided into biliary atresia and non-biliary atresia according to its histopathology. Then, cholestasis severity were analyzed in its liver specimens and divided into mild, moderate and poor groups. Immunohistochemistry were performed to all of the specimens. Spearman Rank test, Eta Contingency, and Coefficient contingency were performed as statistical tests. **Results:** There were 34 subjects consists of 20 biliary atresia and 14 non biliary atresia. The average IFN-γ expression in BA group was 11 ± 3.145 cells whereas in non-BA group was 5.928±1.439 cells. Cholestasis severity in BA group were mild (0%), moderate (5%) and 95% had poor grade whereas in non BA group were 21.43%, 50%, and 28.57% respectively. There was significant correlation between IFN-γ expression and BA incidence (r=0,904; p=0,00). There was significant correlation between IFN-γ expression and cholestasis severity grades (r=0,639; p=0,000). There was significant correlation between cholestasis severity grades and BA incidence (r=0,574; p=0,000). **Conclusions:** IFN-γ was expressed higher in biliary atresia. Biliary atresia had poor cholestasis grade than non-biliary atresia in cholestasis patients.

Keywords— Biliary atresia, IFN-γ, cholestasis severity grade

1. Introduction

Biliary atresia (BA) is a liver dysfunction caused by progressive intrahepatic and extra hepatic obstruction and fibrotic of biliary duct which is marked by cholestasis.[1,2] Almost 90% of this disease occurred in perinatal period, suggested its caused by inflammation process that produced fibrotic and obstruction of biliary duct lumen.[3,4] The incidence of biliary atresia approximately 5 to 20 in 100,000 birth.[1,5]Pathogenesis of biliary atresia is suggested caused by viral infection in the liver which is followed by secondary immunology process. This process leads to progressive inflammation and produces fibro-obliteration of the biliary duct lumen as final stage.[6-9]

Immunology process which is mediated by T cell in biliary duct epithelia produces progressive autoreactive inflammation.[9-10]Interferon gamma (IFN-γ) is a cytokine which is produced by Th1 has main role in producing biliary atresia through autoreactive inflammation.[11,12]Inflammation process which is mediated by IFN-γ runs progressively will be ended as fibrotic of biliary ducts.[11] Animal model study had shown that biliary atresia incidence closely related to high expression of IFN-γ. Expression of IFN-γ increases between day 7^{th} to 14^{th} after Rhesus Rotavirus injection.[13-15]

Cholestasis severity grade in histopathology examination revealed obliteration grades of biliary duct.[16] Cholestasis manifestation will be better by inactivation of IFN-γ in biliary atresia animal model.[11,17]This studyaims to analyze correlation between IFN- expression, cholestasis severity grades, and biliary atresia incidence in neonatal cholestasis.

2. Method

This study was an analytic observational within cholestasis patients 1-12 months as subjects. Liver biopsies were performed to all of the subjects. Then, subjects were divided into biliary atresia (BA) and non-biliary atresia (non-BA) according to its histopathology examination. Cholestasis severity were graded according to histopathology examination to all liver specimens. There were mild, moderate and poor grade. Interferon-γ expression were examined by immunohistology examination. Then, data were analyzed by using Spearman Rank test, Contingency Eta test, and Contingency Coefficient.

3. Result

There were 34 subjects, comprise of 20 biliary atresia and 14 non biliary atresia. Characteristics of these subjects were showed in table 1.

Table 1. Characteristics of subjects

Variable	Biliary atresia (n= 20)	Non biliary atresia (n= 14)	P
Percentage			
Sex			0.051
Male	6 (30%)	9 (64.29%)	
Female	14 (70%)	5 (35.71%)	
Hepatomegaly	20 (100%)	13 (92.86%)	0.232
Splenomegaly	16 (80%)	12 (85.71%)	0.672
Nutritional status			0.457
Normal	14 (70%)	8 (57.14%)	
Wasted	3 (15%)	3 (21.43%)	
Poor	3 (15%)	3 (21.43%)	
Median (interquartile)			
Age (months)	8 (1.75)	5.5 (2.25)	0.186
Duration of sickness (months)	7 (2)	5.5 (2.125)	0.341
Weight (kg)	6.1 (0.96)	4.55 (1.04)	0.007*
Height (cm)	63.5 (4.63)	56 (4.25)	0.005*
Direct bilirubin (mg/dl)	11.09 (2.29)	9.63 (2.94)	0.237
Total bilirubin (mg/dl)	14.49 (5.60)	11.32 (4.47)	0.054
SGOT (mg/dl)	264 (76.88)	204 (63)	0.142
SGPT (mg/dl)	185 (100.88)	151 (50)	0.421

The average of IFN-γ expression in biliary atresia group was 11 ± 3.145 cells whereas in non-biliary atresia

group was 5.928±1.439 cells. There was significant correlation (r=-0.467; p=0.038) between IFN-γ expression and age in BA group (Figure 1).

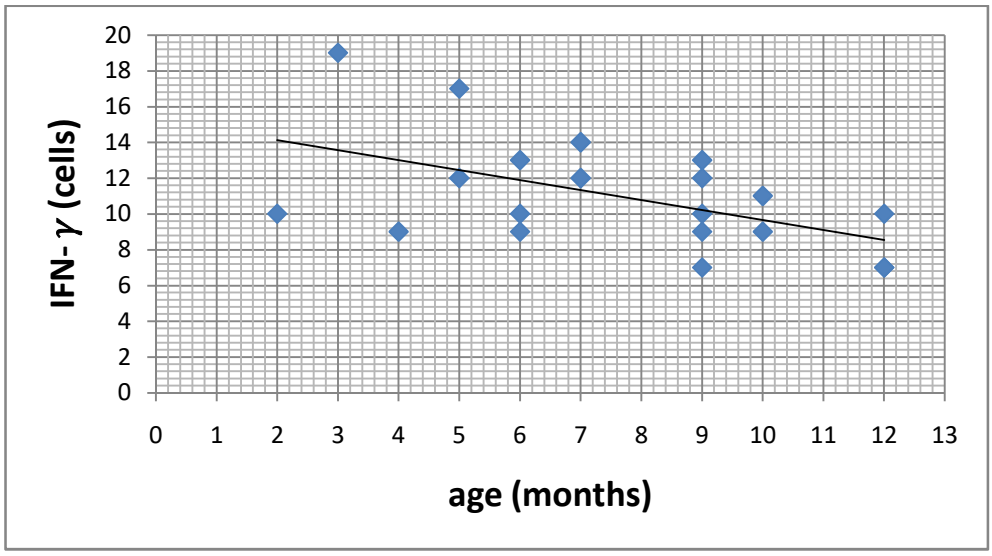

Figure 1. Correlation between age and IFN- γ expression in CD4 lymphocyte

Correlation between IFN-γ expression, cholestasis severity grade, and biliary atresia incidence were described in table 2. Cholestasis severity grades in BA group were mild (0%), moderate (5%), and poor (95%), whereas in non-BA group were 21.43%, 50%, and 28.75%, respectively. There was significant correlation between IFN-γ expression and biliary atresia incidence (r=0,904; p=0,00). There was significant correlation between IFN-γ expression and cholestasis severity grade (r=0,639; p=0,000), and also between cholestasis severity grade and biliary atresia incidence (r=0,574; p=0,000).

Table 2. Correlation between IFN- γ expression, cholestasis severity grade, and biliary atresia incidence

Variable	IFN- γ	Cholestasis severity grade	Biliary atresia incidence
IFN- γ expression			
r	1.000	0.639*	0.904**
p	0.000	0.000	0.000
Cholestasis severity grade			
r		1.000	0.574***
p		0.000	0.00
Biliary atresia incidence			
r			1.000
p			0.000

4. Discussion

Interferon-γ is a substance which is produced by TH1, NK cells and APC as a response to viral infection. This substance has role in innate and adaptive immune response.[18] Investigation of liver biopsy specimens revealed that IFN-γ expression in BA and non-BA groups were significant difference ($p< 0.05$). Interferon - γ expression in BA group was higher than non-BA group. This result was similar to previous study that IFN-γ was expressed excessively in biliary atresia patients than other type cholestasis.[19]

Interferon-γ expression revealed decreasing trend by age in BA group (Picture 1). The highest expression of IFN-γ was at 3 months. This result appropriates to previous study in animal model which shows significant enhancement of IFN-γ in day 7 and then decrease at day 14 to normal level.[20] According to conversion reference, 7 days mice equals to 2-3 months in human.[21] This study had shown, the highest expression of IFN-γ was at 3 months old equals to 7 days in mice. Flowcytometry examination revealed there was 40 times increase of IFN-γ expression in CD4+ lymphocytes at 7th day after induction. Interferon -γ is important effector for TH1 phenotype, thus excessive expression of IFN-γ in the liver consistent to IFN-γ roles in inflammation and obstruction of biliary duct. Elimination of IFN-γ expression will decrease inflammation by decreasing lymphocytes population at triad portal then there will be repairing of icterus.[20]

Interferon-Y has roles in progressivity of biliary duct obliteration through fibrotic phase.[22,23]Cholestasis severity grades by histopathology examination describes obliteration grades of biliary ducts.[16] In this study, there was indirect correlation between IFN-Y and cholestasis severity grade through fibrotic phases.

In this study, there was significant correlation between cholestasis severity grade and biliary atresia incidence. Cholestasis severity grade describes biliary ducts obstruction. Thus, it can describe non direct correlation between cholestasis severity grade and biliary atresia incidence. There was close correlation between cholestasis grades in biliary atresia patients and lumen diameter of obliterated biliary ducts.[16] Cholestasis severity grade in zone 2 and 3 acini closely related to biliary ducts and hepatocytes damage and poor prognosis.[24,25]

5. Conclussion

Interferon-γ is highly expressed in biliary atresia patients. Highest expression is at 3 months age; thus, it is suggested that intervention avoid progressivity of biliary atresia would have better results at this age. Biliary atresia patients have poor cholestasis severity grade than non-atresia biliary patients according to its histopathology.

This study has limited samples. Ideally, liver biopsy is performed by surgical operation. However, this study had given additional evidence regarding hypothesis the role IFN-γin pathogenesis of biliary atresia. It is suggested that this study could overcome future studies in biliary atresia management.

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