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Original Research Article

Biliary Atresia and the Role of Con-Current CMV Infection

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Abstract: ***Introduction***: Biliary atresia (BA) is a progressive fibro-obliterative disorder of the extrahepatic bile ducts, representing the most common indication for pediatric liver transplantation. Despite extensive research, its etiology remains obscure, with proposed mechanisms ranging from viral triggers to autoimmune and developmental anomalies. ***Method***: This is a retrospective study carried over 10 years (Jan 2013-Dec 2022). We investigated in 33 BA patients, with emphasis on 9 cases of cytomegalovirus (CMV) co-infection. ***Result***: Our findings reveal no difference in long term outcome in CMV positive patients. ***Conclusion***: These observations suggest that BA pathogenesis may involve multiple and separate mechanisms affecting the extrahepatic biliary tree warranting further investigation into multiple etiopathogenic pathways.

Keywords: Biliary Atresia, Cytomegalovirus, Jaundice.

INTRODUCTION

Biliary atresia (BA) is a devastating neonatal cholestatic disorder, affecting approximately 1 in 10,000–19,000 live births worldwide, with higher prevalence in East Asia [1]. It is characterized by inflammatory obstruction and progressive sclerosis of the extrahepatic bile ducts, leading to biliary cirrhosis if untreated [2]. While the Kasai portoenterostomy remains the primary surgical intervention, 50–80% of patients eventually require liver transplantation due to disease progression [3].

The etiology of BA remains elusive, with three main proposed categories:

- Perinatal/acquired form (90% of cases): Suspected viral triggers (e.g., reovirus, rotavirus, CMV) inciting an autoimmune response against bile duct epithelium [4–6].
- Embryonic/fetal form (10%): Associated with congenital anomalies (e.g., polysplenia, cardiac defects) [7].
- CMV-associated BA: Distinct subgroup with IgM-positive CMV infection with possible worse prognosis [9].

Recent studies highlight the potential role of CMV in BA pathogenesis, with reported CMV positivity rates ranging from 15–40% [8, 9]. CMV may act via direct cytopathic effects or immune-mediated bile duct injury [10]. However, the inconsistent association between CMV and BA outcomes raises questions about its precise role.

In this study, we examined whether CMV co-infection correlate with adverse clinical outcomes.

MATERIALS AND METHODS

Study Design and Patient Selection

A retrospective analysis was conducted on all BA patients who had Kasai portoenterostomy at Tygerberg Hospital between Jan 2013 to Dec 2022 (n=33). Local ethics committee certified the study: C11/2654.

Inclusion Criteria:

- Confirmed BA diagnosis via intraoperative cholangiography and histopathology.

Exclusion Criteria:

- Incomplete clinical/histological records.
- Syndromic BA (e.g., BASM – biliary atresia splenic malformation).

Clinical and Laboratory Data Collection

Demographic, preoperative (age at surgery, biochemical markers), and postoperative (native liver survival, transplant-free survival) data were extracted (table.1). CMV status was determined via serum PCR (Polymerase Chain Reaction) (COBAS® AmpliPrep/COBAS® TaqMan CMV Test, Roche Diagnostics).

Histopathological Analysis

All resected tissues (fibrotic plate at porta hepatis, Liver biopsy and GB) were fixed in 10% formalin, paraffin-embedded, and stained with: Hematoxylin & eosin (H&E), Masson's trichrome (fibrosis assessment), and Immunohistochemistry for CMV (via monoclonal anti-CMV pp65).

Histological features evaluated was extrahepatic bile ducts: Degree of inflammation (lymphocytic infiltrate), Bile ductular proliferation, fibrosis stage (Scheuer classification).

Statistical Analysis

Survival analysis employed Kaplan-Meier curves (log-rank test). The value of significance was set at $p<0.05$. Analysis used standard IBM package SPSS v26.

RESULTS

Patient Characteristics

Of 33 BA cases identified, all had tissue available for examination. Median age at Kasai was 52 days (IQR: 34–98). CMV-PCR positivity was noted in 9/33 cases (27.3%), with one patient requiring ganciclovir for high viral load (≥10,000 copies/mL).

Histopathological Findings were as follows:

- Extrahepatic Bile Ducts at porta hepatis:
- All cases showed near-complete luminal obliteration with dense fibrosis.
- Chronic inflammation (CD3+ T-cell predominance) and bile ductular proliferation at the portal plate.
- No CMV inclusion bodies were identified immunohistochemically in the liver, the GB, and the portal plate.

Clinical Outcomes:

Minimum follow-up was 2.5 years. In that time 12/33 (36%) retained native liver, 4/33 (12%) required transplantation, and 17/33 (50%) who were not suitable for transplantation (due to poor socio-economic status) died from liver failure or portal hypertension.

CMV status did not predict transplant-free survival ($p<0.62$).

DISCUSSION

BA is characterized by inflammatory obstruction and progressive sclerosis of the extrahepatic bile ducts, leading to biliary cirrhosis even if managed surgically.

This study reveals one important observation with regard to CMV infection.

There appears to be a CMV discordance meaning that despite high CMV positivity (27%), no CMV-specific histological features were identified. In medical literature there is some evidence that CMV is as common in neonatal jaundice as in BA cases [8].

Our data question the "two-hit" hypothesis (viral trigger + autoimmunity) because

Alternative Mechanisms should be considered such as; ductal plate malformation with variable GB involvement reflecting developmental arrest [10]. Ischemic injury due to aberrant hepatic artery flow could explain regional unevenness [11].

Limitations and Future Directions

- Sample Size: Small cohort limits subgroup analyses. Multicentre collaboration is needed at national level.
- CMV Detection: PCR detects systemic infection but not liver tissue-specific CMV activity. In situ hybridization could clarify this.

- Prospective Validation: A longitudinal design tracking CMV viral load and immune markers pre/post-Kasai would strengthen causality.

Table of patients

Gender	DOB	Age at Surgery	OTHER DE	CMV result (and how)	LFT at	LFT at	Death/TRANSPLANT (cause)	GB histology
M	07/10/2022	102		CMV +ve			Died	Yes-fibrosed
F	04/07/2022	45		CMV +ve			Died	NO
F	12/06/2023	34		CMV +ve & Syphilis +ve			Died	Yes:fibrosed
M	27/06/2017	94		PCR +ve			06/2021 - tranplant	Yes: normal
F	05/03/2018	98		IGM +VE, PCR +VE			Alive- 10/2021	Yes: Normal
M	01/03/2011	83		negative			08/2011-? Died	Yes-fibrosed
F	01/05/2006	85		negative			02/2022 - Alive (high Conj Bili at 45 umol)	Yes-fibrosed
F	13/09/2011	100		negative			Alive on 03/2022	YES-fibrosed
M	26/11/2010	122	ARM	negative			LAST ENTRY=20/05/2011 = Died	Yes-fibrosed
F	09/02/2006	91		negative			TRASPLANT LAST ENTRY= 26/10/2006-Died	Yes-fibrosed
F	04/11/2003	122		negative			DEAD: 02/03/2005	YES-fibrosed
F	11/02/2004	69		negative			09/2021- Alive	NO
M	10/05/2011	69		negative			03/2017 - DEAD	Yes-fibrosed
M	25/03/2009	92		negative			LAST ENTRY 12/10/11= DEAD	Yes-fibrosed
F	08/01/2022	34		negative			Alive	YES-fibrosed
F	15/07/2015	33		Negative			Tranplanted - alive 25/10/21	yes: fibrosed
M	04/05/2022	96		negative			114CB at 06/10/22	yes: fibrosed
M	23/02/2010	122		negative			LAST ENTRY = 10/2010 - DEAD	Yes: Fibrotic
F	11/01/2011	83		negative			LAST ENTRY- 8/11/2012 = DEAD	Yes: fibrotic
M	14/03/2010	122		negative			Transplant: 2013	Yes: fibrotic
M	14/04/2005	68		negative			TRANSPLANT : 18/03/19	Yes: normal
F	30/07/2013	92		negative			Dead - 04/2014	Yes: normal
M	06/08/2008	122		negative			LAST ENTRY = 11/2009 - DEAD	Yes: normal
M	26/10/2004	123		negative			10/2018 ? DEAD	Yes: normal GB
F	10/09/2009	88		negative			TRANSPLANT :2013	Yes: normal GB
F	24/12/2012	77		negative			10/2014- DEAD	Yes: normal GB
M	27/12/2015	51		pcr + ve			LAST ENTRY = 11/2020 - DEAD ?	Yes: Fibrotic
M	18/03/2017	96		PCR +VE			Died (END STAGE LIVER FAILURE); 28/05/2018	Yes: normal GB
F	02/10/2020	59		pcr +ve			1/2021- Died	Yes: Fibrotic
M	02/08/2019	44		pcr -ve			06/11 - Alive	YES: Normal
M	19/05/2007	153		positive			LAST ENTRY= 27/08/2009 =DEAD	Yes-fibrosed
M	20/09/2023	39		Syphilis +ve			DIED	YES: Fibrotic
F	26/05/2021	48		positive			DIED	YES: Fibrotic

CONCLUSION

This study demonstrates that CMV co-infection did not influence histopathology or outcomes, suggesting its role in BA may be incidental rather than causative. These findings underscore the need to re-evaluate BA's pathogenesis with particular attention to non-immune mechanisms (e.g., vascular, developmental) in subsets of patients.

Further research should integrate multi-omic approaches (transcriptomics, proteomics) to identify distinct BA endotypes which may explain different outcomes in different geographical regions.

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