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Reduced presentation of Biliary Atresia during the COVID-19 lockdown – a population based observational study

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Abstract

Objective

The aim of this study was to assess whether there has been a change in presentations of Biliary Atresia (BA) in England and Wales during the first and second COVID-19 lockdowns (January – June 2020 and 2021).

Design

This population study assessed all confirmed cases of BA, from January 2020 to December 2021 across the 3 UK paediatric liver centers originating from England and Wales. Data was then compared to the incidence of confirmed BA cases from January – December 2017, 2018, and 2019.

Results

During January – June 2020 and 2021, there were only 8 and 12 presenting cases of BA in England and Wales, compared to 16, 13 and 18 for the same time periods in 2017, 2018 and 2019 respectively. This difference was significant in a two-sided t-test for 2020 ($p = 0.035$) but not for 2021 ($p = 0.385$). There was no difference in the mean days to Kasai procedure in January – June 2020 and 2021 compared to 2017-2019, however average time to Kasai after the lockdown periods was significantly higher.

Conclusions

There was a significant reduction in the presenting cases of BA during the first COVID-19 lockdown, with an increased time for BA referrals after the pandemic lockdowns were lifted in England and Wales.

What is known

- Biliary Atresia (BA) is a destructive inflammatory condition of unknown aetiology that results in fibrosis and obliteration of the biliary tract in neonates
- It is the commonest indication for liver transplantation in children worldwide
- Early referral and surgery with the Kasai procedure (at less than 60 days) substantially improves long-term
- There are an average of 50 cases of BA in England and Wales every year

What is new

- There was a significant reduction in the number of presenting BA cases from January – July 2020 during the COVID-19 pandemic.
- This may be associated with social distancing during the first COVID-19 lockdown suggesting an environmental/viral aetiology

Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic affecting over 635 million people worldwide (1). The United Kingdom (UK) is considered a hotspot for the disease, with 24 million confirmed cases and over 211,000 deaths within the country to date (12th November 2022) (1, 2).

Biliary Atresia (BA) is the commonest surgical cause of cholestasis in infancy, affecting 1 in 17000 live births in England and Wales (3, 4). The condition is caused by a destructive inflammatory process of unknown aetiology that results in fibrosis and obliteration of the biliary tract. Initial treatment of BA is surgical, with a Kasai portoenterostomy that aims to restore the bile flow (5). However, if the procedure is not successful and/or liver fibrosis progresses and cirrhosis starts to develop, liver transplantation (LTx) is necessary, and BA is the main indication for liver transplantation in children worldwide. Of importance is that an increased age at surgery has a progressive and sustained deleterious effect on the results of the Kasai operation. It is well established that early diagnosis and surgical intervention is associated with improved long-term outcomes and a reduced risk of subsequent LTx (6-8).

The UK has three paediatric liver centres that specialise in the management of BA: King's College Hospital (KCH), Birmingham Women's & Children's Hospital (BWCH) and Leeds Children's Hospital (LCH). Data from cases arising in England and Wales has been collected within a national registry for over 20 years with an average of about 40 BA cases every year. However, recent observations from clinicians within these centres have suggested a reduction in the number of cases during the COVID-19 lockdowns (from January to June 2020, January – June 2021) (9).

This is concerning given the deleterious association between late presentation of the condition and the risk of LTx. We sought to define this observation by comparing the incidence of BA to prior years.

Methods

Study population

Confirmed cases of BA were identified from January 2020 to December 2021 at the 3 UK paediatric liver centers (KCH, BCH and LCH). This period covered the first and second COVID-19 lockdowns in the UK (March 2020 – June 2020 and January 2021 – March 2021). Data were then compared to the incidence of confirmed BA cases, as well as the time to Kasai procedure during the same times periods in 2017, 2018 and 2019 as documented within the Biliary Atresia National Registry (BANR) – an approved national registry database. Only patients from England and Wales were included in this analysis, as data in the NBAR were only collected for these regions. Cases of BA were grouped according to date of patient birth.

Outcome measures

The following data points were collected: all children diagnosed with BA in 2020 and 2021 by month, the date of the child's presentation, date of their Kasai procedure and details of the child's presentation.

Our primary outcome was the incidence of BA compared to the same periods in 2017 – 2019. Our secondary outcome was age at Kasai procedure in 2020 and 2021 compared to 2017 – 2019.

Statistical Analysis

The number of BA cases presenting in January to June 2020 and 2021 were compared with the number of cases presenting in January to June 2017, 2018, and 2019 using a chi-squared test of proportions. A similar method was used for July – December 2020 and 2021 (compared to the same time periods of July – December 2017, 2018, and 2019). Under the null hypothesis

that there was no difference between 2020/2021 and the other years, the proportion of all cases presenting in 2020/2021 would be one quarter of the total number of cases.

The mean time to Kasai procedure for cases presenting in January to June 2020 and 2021 were compared with the mean times to Kasai procedure in January to July 2017, 2018, and 2019 using a t-test.

All analyses were performed using Python Anaconda statistical software. A p value<0.050 was considered statistically significant in our analysis.

Ethical Approval

A Research Ethics Committee opinion was sought and in view of the report, it was determined that a formal ethics review was not necessary. There was no funding for this study.

Results

Table 1 details the number of children presenting with BA in January - June 2020 and 2021 compared to 2017 - 2019. There were 8 and 12 presenting cases of BA across the 3 centers in England and Wales for 2020 and 2021, compared to 16, 13 and 18 for 2017, 2018 and 2019 respectively. A chi-square test comparing the expected proportion of cases presenting in 2020 with the observed proportion was statistically significant: p = 0.035. No significant difference was observed for January – June 2021 (p = 0.385). Furthermore, there was no significant difference in total annual number of BA cases for the years with COVID lockdowns (2020 and 2021) compared to the preceding years.

We further assessed to see if there was a difference in the age of the children when the Kasai procedure was performed. Table 2 details the average age at Kasai procedure for each of the respective time periods. While the mean days to Kasai procedure was no different in January – June 2020 and 2021 compared to 2017-2019 (59.8 and 46.2 vs. 53.7 days), time to kasai (days) was longer in July – December (after the pandemic lockdowns) in both 2020 and 2021 compared to the same time periods in 2017 – 2019 (53.2 and 57.3 vs. 43.6, p = 0.005).

Discussion

Our observational study shows a significant reduction in the number of presenting BA cases from January – June 2020 (coinciding with the 1st COVID-19 lockdown). A total of 8 BA cases were observed, compared to an expected number of ~15 (taken from the average cases seen during the same time periods in 2017, 2018 and 2019). While there was no significant increase in the time to Kasai during the lockdown period, it was noted that following both the 1st and 2nd COVID-19 lockdowns there was an increased time for BA infants to undergo a Kasai procedure.

While correlations between the COVID lockdown and delays in new BA cases have been reported amongst Dutch centres, we are the first study to have fully detailed, from a national registry, the reduced presentation of BA during the COVID-19 pandemic (10). This is of concern given the seriousness of the condition, with BA being the most common indication for paediatric liver transplantation (11). Treatment is time-sensitive with a Kasai portoenterostomy. If this is successful, the procedure transforms the outlook and delays the need for urgent LTx for many years. Failure to treat the condition at all leads to progressive liver fibrosis, cirrhosis, and failure, with poor survival, and historically, death occurring by 2 years in most cases (12).

There seem to be two potential hypotheses to explain these observations.

Firstly, was there simply a reduction in timely referrals of BA to the centres? The COVID-19 lockdown has caused significant changes in the organisation of NHS services; with reconfiguration to manage surges in the acutely unwell adults. Subsequent media campaigns have focused on the public to stay at home and prevent infection spread. As a result, some observational reports have shown reduced presentations of children to both primary care and the emergency department (13-16). This has resulted in subsequent changes to the NHS 111 algorithm (a triage helpline in the UK) and a campaign by the Royal College of Paediatrics and

Child Health to triage children with either red flag (high risk) or amber flag (intermediate risk) symptoms for medical review. The effectiveness of this subsequent campaign is not known.

An observational study of seven UK paediatric emergency departments in the Lancet (Roland et al.) aimed to identify the number of children with delayed presentations. The study further subanalysed to determine the proportion of these delays that were due to hesitance of parents in attending vs. the proportion that were due to advice from primary care staff or NHS 111 referrals (17). The authors reported that most patients (1262, 93.5%) did not have a delay in their presentation. In 40 (3.0%) cases, parental delay was thought to be relevant, and in 11 (0.8%), advice from a health-care professional or NHS 111 was thought to have caused the delay. No cause could be found in the remaining 36 (2.7%). Red-flag symptoms were reported in 81 (6.0%) patients. Of these, only 2 (1.5%) were felt to have been delayed. These results provide some reassurance that significant paediatric conditions are not being missed within the COVID-19 lockdown. The extent to which this is due to the aforementioned changes to triage guidelines is unknown.

We must further consider whether the recognition of BA by health professionals has been impaired. BA presents with neonatal jaundice, often a prolongation of physiological jaundice. Affected children can be identified by assessment of stool colour, with the characteristic pale stools being present by 2 weeks and universal amongst cases by 1 month of age (18). It has been well referenced in the literature that professionals do not recognize the pale stools of BA reliably (19-21). With consultations having been reduced and shifted to being telephone and virtual, the sensitivity of diagnosing BA may have been deleteriously affected, leading to the reduced referrals of BA that we have observed.

Our second explanation for the reduced presentation of BA could be an actual reduction in its incidence. The aetiology of BA is unknown, but genetic, developmental and environmental factors may exist (22). One possible link is with perinatal viral infection, with potential

associations with rotavirus (23), reovirus (24), Epstein Barr Virus (EBV) (25) and Cytomegalovirus (CMV) (22), Perinatal CMV associated BA has been identified in 10% of BA cases in the UK, but a far higher proportion from Asian centres with a more delayed presentation, increased liver fibrosis and a poorer outcome to surgery than isolated, non-CMV BA (26, 27).

Observational evidence from the Royal College of General Practitioners has shown a reduction in transmissible viral infections during the COVID-19 lockdown. In the week ending 6th October 2020, cases of common cold were 1.5 per 100,000. This is in comparison to a rate of 92.5 per 100,000 during the same period last year. The incidence of non-COVID related illnesses was similar, with a rate of 131 per 100,000 people, compared to 303 per 100,000 last year (28). In sub-analyses, rates of infectious conditions such as chickenpox and viral gastroenteritis have also fallen to significantly lower incidences. It could be considered this is due to the protective measures e.g. social distancing, increased hygiene Such measures could have further reduced the transmission of the implicated viruses in the pathogenesis of BA.

Associated with this hypothesis, from among children developing liver disease during the covid period, there was an observed epidemic of adenovirus in children under 6, who also contracted simultaneous other viruses including adenovirus associated virus AAV2. In this case, following a period of reduced risk of exposure and without prior immunity, younger children received viruses simultaneously at a critical time, perhaps developmentally leading to severe life-threatening hepatitis. An analogous situation of population low exposure followed by intense exposure may also apply for the agent(s) associated with BA, also limited by the early post-natal period of developmental susceptibility (29, 30).

There are several limitations to this study. This is an observational study conducted across the three liver centres in the UK and included BA cases from England and Wales only, with small available study numbers. It would have been beneficial to extend our analysis to cases from

Scotland and Northern Ireland to assess if presentations of BA are also reduced within these regions of the UK. Unfortunately, we do not have historical data for the number of BA cases from these regions for 2017 – 2019. Furthermore, we could improve the analysis by gathering supplementary variables, including the time to presentation, and whether there was any delay in receiving community services during the COVID-19 lockdown. An important denominator that is missing is the number of patients referred with neonatal conjugated hyperbilirubinemia. By exploring this variable, we could gain further insight as to whether there has been a decrease in referrals or a reduction in incidence of BA during this COVID-19 lockdown.

Overall, our observational study has demonstrated a significant reduction in the number of presenting BA cases from January – June 2020 (coinciding with the first COVID-19 lockdown). Given the unknown aetiology of BA, and the deleterious association between delayed BA presentation and outcomes, further investigations across international centres is required to assess if this observation during the COVID-19 lockdowns has been replicated across paediatric hepatology centres worldwide. Furthermore, as cases of COVID-19 reduce, assessment to see whether there is a late surge in BA cases will help determine whether lockdowns have affected the referrals or incidence of the condition.

Abbreviations

BA – Biliary Atresia

COVID-19 – Coronavirus disease 2019

Liver Transplantation - LTx

UK – United Kingdom

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Table 1: Number of presenting cases of BA from 2017 – 2021

Year	Number of BA Cases	Overall p-Value
January – June		
2017	16	0.064
2018	13	
2019	18	
2020*	8	
2021†	12	
Annual (January – December)		
2017	32	0.406
2018	26	
2019	44	
2020	27	
2021	32	

BA; Biliary Atresia. *January – June 2020 1st COVID-19 lockdown in England and Wales, †January – June 2021 2nd COVID-19 lockdown in England and Wales.

Table 2: Comparison of time to Kasai before and after the COVID-19 lockdown periods

Time period 1	Time period 2	Mean Kasai delay in time period 1	Mean Kasai delay in time period 2	p-value from t-test for a difference between means
Jan-Jun 2017-2019	Jan-Jun 2020 (Lockdown 1)	53.7	59.8	0.669
Jan-Jun 2017-2019	Jan-Jun 2021 (Lockdown 2)	53.7	46.2	0.135
Jul-Dec 2017-2019	Jul-Dec 2020 (Post-Lockdown 1)	43.6	53.2	0.116
Jul-Dec 2017-2019	Jul-Dec 2021 (Post-Lockdown 2)	43.6	57.3	0.001