The bilious bowel: the relation between bile and bowel in development of biliary atresia and liver fibrosis. An explorative study

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To investigate the origin of BA we will assess which TLR(s) is/are activated. To test the hypothesis that during development of BA and associated liver fibrosis there is a *leaky gut* and/or a change in microbiome we will use human material to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON44888

Source
ToetsingOnline

Brief title
BiBoBa

Condition

- Hepatobiliary disorders congenital
- Abdominal hernias and other abdominal wall conditions
- Hepatic and hepatobiliary disorders

Synonym
liver fibrosis - scarring of the liver

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: biliary atresia, gut microbiota, gut wall integrity, liver fibrosis

Outcome measures

Primary outcome

Clearance of jaundice, transplantation-free survival

Secondary outcome

Gut microbiota in faeces, serum levels of Zonulin and tight

junction/translocation markers e.g. ZO-1, Claudin-1, 2 and 3,

Lipopolysaccharide Binding Protein (LBP) and CD14. Secondary end points:

histological assessment of both the tight junction complex in the small bowel

as well as liver fibrosis as present in routine clinical pre- or preoperative

liver biopsies or as assessed using Fibroscan and/or APRI

Study description

Background summary

Biliary atresia (BA) is a rare disease of infancy. An unknown (infectious?) event leads to bile duct scarring and liver injury. Only surgery - reconstructing bile ducts via the so-called Kasai procedure - can postpone liver scarring necessitating transplantation. Surgery is successful in re-establishing bile flow in some 55% of cases. However, despite successful surgery liver fibrosis rapidly progresses and liver failure ensues. A liver transplantation will be necessary in some 70% of children with BA. BA is the main indication for pediatric liver transplantation. As yet the driving force of the rapidly developing fibrosis is unknown. Identifying the pro-fibrotic factors at work in children with biliary atresia might offer novel therapeutic avenues to prevent or postpone liver transplantation. Results from these

studies might also be applicable to other hepatobiliary diseases in children as well as in adults.

The liver is continuously exposed to gut-derived products. Healthy individuals develop tolerance. Susceptible neonates might fail to develop tolerance or be exposed to higher level of danger signals due to a *leaky gut*. Scarring of bile ducts diminishes bile flow. The absence of bile in the bowel changes the gut microbiome and increases bowel permeability, inducing translocation and further liver scarring: a vicious circle.

Activation of receptors on immune cells and bile duct cells (Toll-like-receptors, TLR) by exposure to danger signals (e.g. bacterial or viral products) induces liver scarring (*fibrosis*). Different TLRs respond to different pathogens. Investigating which TLR is activated points towards the pathogen inducing BA.

Many consider BA the result of an unknown perinatal (infectious?) insult, leading to inappropriate immune activation aimed at bile duct cells. I hypothesize that BA and BA associated liver fibrosis is due to immune over-activation, triggered by persistent exposure to gut-derived products. This *leaky gut* may be due to *tight junction* dysfunctioning (gaps in the bowel) and/or a change in microbiome.

Study objective

To investigate the origin of BA we will assess which TLR(s) is/are activated. To test the hypothesis that during development of BA and associated liver fibrosis there is a *leaky gut* and/or a change in microbiome we will use human material to assess translocation markers in blood, bowel tight junction functioning, and the gut microbiome. Data will be related to clinical outcomes such as grade of fibrosis in pre-/preoperative liver biopsies, clearance of jaundice and transplantation-free survival. Data from BA patients will be compared to data from patients with other hepatobiliary diseases such as patients with choledochal malformation, Progressive Familial Intrahepatic Cholestasis (PFIC) and Alagille*s disease as well 30 healthy controls (children with inguinal hernia or jejunal atresia - who are the same age as children with biliary atresia. We will also compare BA patients who need to undergo liver transplantation (most of them before their fifth year) and those who survive for a prolonged time with their own liver. This will shed light on the effects of the microbiome and bowel wall integrity on the progression of liver fibrosis.

Study design

prospective study, explorative in nature

Study burden and risks

There will be no risk or burden for the children, who will not have to undergo extra biopsies or venapunctures for this research. Collection of faeces from the diaper will also not be a burden. During the Kasai procedure as well as during surgery for choledochal malformation a Roux Y reconstruction (anastomosis between two parts of small bowel in Y-form) is performed, which makes it easy and without any risk to obtain a small part of small bowel. Obtaining a small piece of bowel during the performance of a partial external biliary diversion (a *bile-stoma* constructed of a loop of bowel anastomosed between the gallbladder and the skin) in children with PFIC/Alagille is also without any risk or burden for the same reasons. Obtaining the jejunal tissue during the closure of the ostomy in children with jejunal atresia is also without risk or burden, as the piece of small bowel is otherwise discarded. Liver biopsies are routinely obtained during or prior to the Kasai procedure as well as during other hepatobiliary surgery for clinical reasons. This also holds true for obtaining ascites and a mesenteric lymph node.
Collecting faeces from the diaper of a child undergoing surgery for inguinal hernia is also not a burden. CHildren undergoing surgery for inguinal hernia always get an I.V. line prior to surgery: blood will be collected from the I.V. This wil not be a burden or a risk.

As biliary atresia and most of the other aforementioned diseases are diseases only occurring in young children, this study can only be performed in this patient group of young children

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

children with hepatobiliary disease necessitating surgery

Exclusion criteria

Adults, congenital bowel defects or abdominal wall defects, extreme prematurity/very low birth weigth

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-09-2015

Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	14-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL53531.042.15
Other	volgt