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**Constipation in (early) infancy and childhood : pathogenesis and diagnostic procedures**

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# **Chapter 1**

Outline of the thesis



## Outline of the thesis

The first stool in healthy term born infants, meconium, is usually passed within the first 24 hours of life and approximately 99% of these infants pass their first stool within 48 hours after birth<sup>1,2</sup>. Delayed passage of the first stool is relatively common in very low birth weight infants, and prematures  $\leq 32$  weeks gestation (20-57%). This is probably due to physiological immaturity of motor function, lack of triggering of enteral feeding on gut hormones and more viscous meconium compared with full-term infants<sup>3,4</sup>. In the absence of other clinical findings it is generally accepted that there is no need for extensive evaluation even up to 2 weeks of age<sup>2</sup>.

A delay in the passage of meconium in combination with clinical findings such as vomiting, irritability and abdominal distension, is an alarm symptom suggesting intestinal obstruction due to Hirschsprung's disease (HD), bowel atresia, meconium ileus or meconium plug syndrome.

HD is a developmental disorder of the enteric nervous system characterized by an absence of ganglion cells along a variable distance of the distal intestine from the internal anal sphincter. About once per 5000 live births, constipation is caused by HD<sup>5</sup>. More than 90% of the infants with HD fail to pass meconium within 24 hours after birth which can lead to severe constipation, abdominal distension, enterocolitis, toxic megacolon and even death. Therefore it is of clinical importance to differentiate between Hirschsprung's disease and functional constipation in these young infants. Differentiation is possible by detecting the presence or absence of the rectoanal inhibitory reflex (RAIR), using anorectal manometry.

The presence of the RAIR is important for normal defecation. The RAIR is a transient relaxation of the internal anal sphincter. When stool arrives in the rectum, filling of the rectum leads to stretch of the rectal wall with subsequent triggering of the RAIR. A normal developed enteric nervous system is necessary for a normal RAIR. Impaired or absent relaxation of the internal anal sphincter hampers the evacuation of stool leading to severe chronic constipation as described in HD<sup>6</sup>.

**Chapter 2** describes in detail the symptomatology, pathophysiology, genetical background and tools to diagnose HD.

Besides children with Hirschsprung's disease, there is a subgroup of preterm and term neonates with defecation problems directly after birth. These infants present often with a delayed passage of meconium ( $> 24$  hours after birth), abdominal distension and feeding problems<sup>7</sup>. However, these gastrointestinal

symptoms resolve in the following weeks after birth. The exact reason for these transient defecation problems is unclear. One possibility could be that the components responsible for normal motility have not been developed properly. Recently, a study demonstrated that transient defecation problems may result from a delayed maturation of interstitial cells of cajal (ICC). ICC function as pacemaker cells coordinating the electromechanical activity of the gut<sup>8,9</sup>. To what extent this delayed maturation in ICC also affects the RAIR is so far unknown. Therefore, we first evaluated whether ICC play a role in the triggering of the RAIR. We designed an animal study in which we investigated the role of ICC and nitric oxide in the inhibitory neurotransmission of the murine internal anal sphincter (**chapter 3**). In addition, we evaluated whether the RAIR is indeed absent in these children with an episode of constipation. Therefore, we investigated the presence of the RAIR in premature neonates with a transient delayed meconium production (> 48 hours) (**chapter 4**).

From the above chapters it is obvious that the RAIR is an important reflex pattern, necessary for normal defecation. Especially in children with delayed meconium production, it is therefore of great importance to detect possible abnormalities in the presence or absence of the RAIR. Clearly, this implies that the age at which the RAIR is matured has to be identified. A normal developed RAIR to rectal distension has been shown in term and premature infants older than 30 weeks' postmenstrual age (PMA)<sup>10</sup>. However, it is unknown if the RAIR is matured in very premature infants (< 30 weeks' PMA) (**chapter 5**).

Anorectal manometry in the neonate offers a non-invasive diagnostic test for identifying the RAIR. It measures pressures in the anorectal region evaluating internal and external sphincter function. In addition to anorectal manometry, two other tests are also employed in the diagnostic work-up of patients suspected for HD. A contrast enema showing a transitional zone, which is the critical feature to suspect HD and to determine the length of the aganglionic segment. And rectal suction biopsy (RSB), which shows an elevated acetyl cholinesterase activity and an aganglionosis in case of HD. There has been considerable debate about the most appropriate diagnostic approach for HD, since all tests produce low sensitivities and low specificities<sup>11-14</sup>. Since it is not clear what test is the most accurate one in the diagnostic work-up of HD, different approaches are used in different hospitals. A systematic review was conducted to determine and compare

the diagnostic accuracy between contrast enema, anorectal manometry and rectal suction biopsy in infants suspected of HD (**chapter 6**). Subsequently, a study was conducted in which we prospectively compared the diagnostic accuracy of contrast enema, anorectal manometry and rectal suction biopsy in infants suspected of HD (**chapter 7**). Based on these results we can offer clinicians the best diagnostic work-up for HD and consequently prevent performing unnecessary tests.

From the above chapters it is clear that diagnosis of neonates and infants with HD and with transient defecation problems is often difficult, but as well in children at later age with functional constipation, diagnosis may be difficult. Functional constipation is a common problem in toddlers and older children, accounting for 3-10% of the visits to a paediatric practice. Although the medical history and physical examination form the corner stone for the diagnosis of constipation, a plain abdominal radiograph is frequently used to confirm the presence of retained stool or enlargement of the colon or rectum<sup>15-17</sup>. Several scoring methods have been developed to objectify the severity of constipation on an abdominal x-ray. However, inconsistent data exist with reference to the value of an abdominal x-ray in the diagnosis of constipation<sup>18,19</sup>. In **chapter 8** the value of a new scoring system, the Leech-score, in children with constipation is reported and inter- and intra-observer variability is evaluated.

The measurement of colonic transit time (CTT) is another method to objectify the severity of constipation. This method uses radio opaque markers to localise the delay in colonic transit and is helpful if bowel history is unreliable. It offers more precisely and consistently information about colorectal motor function in defecation disorders<sup>20</sup>. In both adults and children inconsistent data exist concerning the relation between symptoms of constipation and CTT<sup>21-24</sup>. No studies have been performed to investigate the prognostic value of CTT measurement in children with constipation (**chapter 9**). If CTT values can predict success, it is possible to give more clarity to the parents about the course of the child's defecation problems.

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