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

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Chapter 10

Summary & conclusions

Defecation disorders in neonates and children are common in general paediatric practice, and result in 3% of all consultations to a paediatrician. These disorders form the most common complaint in childhood gastrointestinal disease, and can make up to 25% of all consultations to a paediatric gastroenterologist. It is notable that in approximately 40% constipation could be traced back to the first month of life.

After birth, the passage of the first stool (meconium) occurs in 95% within 24 hours and 99% within 48 hours in healthy term infants. This percentage however dramatically drops to 66% in preterm (≤ 32 weeks gestation) and low birth weight (< 2500 grams) infants. In most cases the cause of this delay is unknown. From a clinical point of view, it should alert the clinician as it may be the first sign of a defecation disorder such as Hirschsprung's disease. Therefore, early diagnosis is warranted.

This thesis aimed to investigate the accuracy of different diagnostic procedures in the work-up of (young) infants and children with disturbed defecation. Furthermore, we aimed to clarify the pathophysiology underlying the delayed passage of meconium. The aims of this thesis are described in **chapter 1**.

If delayed passage of meconium presents in combination with clinical findings such as vomiting, irritability and abdominal distension, intestinal obstruction due to Hirschsprung's disease (HD) may be present. 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. This results in disturbed colonic motility and the absence of the rectoanal inhibitory reflex (RAIR). The RAIR is a transient relaxation of the internal anal sphincter elicited by rectal distension. Impaired or absent relaxation of the internal anal sphincter hampers the evacuation of stool leading to severe chronic constipation as described in HD. **Chapter 2** describes the latest findings regarding the pathophysiology, symptomatology, diagnostic workup and treatment of Hirschsprung's disease in infancy and childhood.

Besides children with Hirschsprung's disease, there is a subgroup of neonates with defecation problems directly after birth. These infants often present with a delayed passage of meconium (> 24 hours after birth), abdominal distension and feeding problems. In contrast to HD, these gastrointestinal symptoms resolve in the following weeks after birth. The exact reason for these transient defecation abnormalities 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 abnormalities may result from a delayed maturation of interstitial cells of Cajal (ICC). ICC function as pacemaker cells coordinating the electromechanical activity of the gut. To what extent this delayed maturation in ICC also affects the RAIR is so far unknown. In **chapter 3** we studied the role of ICC in the inhibitory neurotransmission of the murine internal anal sphincter. The relaxation of the IAS to electrical stimulation was measured *in vitro* in an organ bath and showed that there was no difference in relaxation of the IAS between mice lacking ICC compared to controls. However, *in vivo* experiments showed that the RAIR in response to rectal distension was clearly diminished in mice lacking ICC. This suggests that an intact network of ICC in the IAS is necessary for a normal RAIR, and provides evidence that ICC may be involved in the afferent limb of the RAIR. Therefore, dysfunction or delayed maturation of ICC may lead to an impaired anal sphincter relaxation and may thus be involved in rectal evacuation disorders.

To evaluate this hypothesis, the presence of the RAIR was determined in premature neonates with a transient delayed meconium production (> 48 hours), as described in **chapter 4**. Anorectal manometry was performed in 10 preterm infants (range postmenstrual age (PMA) 28-30 weeks) with delayed passage of meconium (range 48-105 hours). A normal RAIR could be elicited in all infants studied, suggesting that delayed meconium passage in this subgroup of children is not related to the absence of a RAIR. 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 of great importance to detect possible abnormalities in 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' PMA. However, it is unknown if the RAIR is matured in very preterm infants (<30 weeks' PMA). Therefore, we evaluated the maturation of the RAIR in preterm infants in **chapter 5**. Anorectal manometry was performed in 16 healthy preterm neonates (range PMA 27-30 weeks) and a normal RAIR could be elicited in 13 (81%) infants. These findings suggest that the majority of preterm infants older than 26 weeks' PMA have a normal RAIR.

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. At contrast enema of the colon, a calibre change with a dilated normal colon to a narrowed aganglionic bowel is typically present. Lastly, a rectal suction biopsy is taken to evaluate cholinesterase activity and the presence or absence of enteric neurones. There has been considerable debate about the most appropriate diagnostic approach for HD. Therefore, we searched the literature and conducted a systematic review to determine and compare the diagnostic accuracy between contrast enema (CE), anorectal manometry (ARM) and rectal suction biopsy (RSB) in infants suspected of HD (**chapter 6**). 24 studies met our inclusion criteria and all had a retrospective design. This review showed that RSB was the most accurate test having both the highest mean sensitivity (93%) and mean specificity (98%). Sensitivity and specificity of ARM (91% and 94% respectively) was similar to that of RSB, whereas CE showed a significantly lower sensitivity and specificity (70% and 83% respectively).

Subsequently to this review, we conducted a prospective study in which the diagnostic accuracy of CE, ARM and RSB in infants suspected of HD was compared (**chapter 7**). 111 consecutive infants with delayed passage of meconium and suspected of HD were enrolled in the study and underwent all three tests (CE, ARM and RSB). HD was found in 28 out of 111 patients (25%). RSB had the highest sensitivity (93%) and specificity (100%), but values were not significantly different from CE (76% and 97% respectively) and from ARM (83% and 93% respectively). Inconclusive test results occurred most often with ARM and was lowest with RSB. This suggests that RSB is the most accurate test to diagnose Hirschsprung's disease.

From the above chapters it is clear that diagnosis of children with HD and children with transient defecation problems is often difficult, but also in children at later age with functional constipation, diagnosis may be difficult. 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. However, inconsistent data exist concerning the value of a plain abdominal radiograph in children with functional constipation. In **chapter 8**, we assessed intra- and inter-observer variability and determined the diagnostic accuracy of a new scoring system

(Leech-method) to identify children with functional constipation. 89 children with functional gastrointestinal disorders were included in the study. Based on clinical parameters, 51 fulfilled the criteria for functional constipation, 7 and 31 children fulfilled the criteria for functional abdominal pain, and functional non-retentive faecal soiling, respectively and were classified as controls. Intra- and inter-observer variability of the Leech method was evaluated by scoring the same abdominal radiograph twice by three observers and diagnostic accuracy of the Leech method was determined by ROC-analysis. The intra-observer and inter-observer variability was high. Furthermore, the Leech score had poor diagnostic accuracy for diagnosing functional constipation and showed a low sensitivity (75%) and specificity (59%) using the optimal cut-off value of 9. This study suggests that a plain abdominal radiograph proves to be of limited value in the diagnosis of functional constipation in children.

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. In **chapter 9** we investigated the relation between symptoms and CTT, and assessed the importance of symptoms and CTT in predicting outcome. At enrolment, 169 consecutive children fulfilled the criteria for constipation and CTT was measured at entry of the study. CTT values were significantly higher in those children with a low defecation frequency and a high frequency of encopresis. However, 50% had CTT values within the normal range. The presence of a rectal impaction at presentation was associated with a better outcome at one year of following and a CTT >100 hours is associated with a poor outcome at one year of following. From both studies we can conclude that scoring a plain abdominal radiograph, either using the Leech-method or with radio-opaque markers (CTT) has a low diagnostic accuracy.

Based on this thesis we would like to advise clinicians in diagnosing HD. If delayed passage of meconium occurs in combination with clinical findings of intestinal obstruction (vomiting, irritability, abdominal distension), HD should be suspected and further evaluation is necessary. As shown in this thesis, there are several options to diagnose HD. RSB showed to be the most accurate test with the highest sensitivity and specificity, although no significant difference was shown compared to ARM and CE.

It should be emphasized though that the optimal diagnostic approach is largely determined by age and should be different in premature infants compared to older infants. In our opinion, in term neonates and older children suspected for HD, RSB should be the first option. A RSB is relatively simple, quick, and efficient and can be considered an incident-free procedure. Although ARM is non-invasive in contrast to RSB, movement artefacts due to agitation of the child quite often make interpretation of the manometric tracing rather problematic. Furthermore, ARM is time-consuming and requires both extensive experience and expertise. The situation in premature infants is rather different, especially as RSB is often too invasive with the risk of infection and perforation. In this fragile group of children ARM showed to be a good but most importantly, a safe diagnostic test for HD. If ARM is not conclusive or if ARM expertise is absent, RSB can be performed in a later stage. Meanwhile, enemas and/or laxatives should be given to relieve colonic distension in these infants. In most cases RSB is possible at term age.

Based on the high specificity and sensitivity, a negative RSB virtually rules out the diagnosis of HD. However, if symptoms persist and clinical suspicion remains high, further evaluation is certainly necessary. If ARM expertise is present in the hospital, ARM is a good option, if not one should refer the patient to a gastrointestinal motility centre. In our opinion the value of a CE in the work up of HD is limited because of its fairly low sensitivity and high radiation exposure. Only if the diagnosis HD has been established, CE might be helpful for the surgeon to assess the localization of the calibre change and thus the presumed length of the aganglionic segment.

