Gastrointestinal motility disorders in children: etiology and associated behaviors
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General introduction and outline of the thesis

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General introduction

Pediatric gastrointestinal motility disorders may present in the neonatal period (e.g. Hirschsprung disease or infantile hypertrophic pyloric stenosis), but may also become present later in childhood. The character, intensity and duration of symptoms may vary widely between patients with these disorders. It is known that gastrointestinal motility disorders can have a significant impact on the child’s life and the lives of his/her family.1-3 Despite the increasing possibilities in diagnostic techniques for gastrointestinal motility disorders, the pathophysiology of pediatric gastrointestinal motility disorders is still poorly understood. In this introduction, general information is provided about three gastrointestinal motility disorders commonly found in children; gastro-esophageal reflux disease, infantile hypertrophic pyloric stenosis, and functional defecation disorders. Furthermore, an introduction into pathophysiological factors and associated behaviors in these pediatric gastrointestinal motility disorders is given.

Gastro-esophageal reflux disease

The passive movement of gastric contents into the esophagus (gastro-esophageal reflux, GER) is a normal physiological mechanism occurring several times a day in every healthy infant, child and adult.4-6 However, when GER causes complaints and/or complications, the diagnosis of gastro-esophageal reflux disease (GERD) may be applicable.7,8 GERD is common in children, with an estimated prevalence of 12.3% in infants and 1% in childhood according to a database survey in the United States.9 Often, medical history in combination with physical examination of the child is sufficient to diagnose GERD. Helpful additional investigations are combined pH-intraluminal impedance monitoring and endoscopy.10 The first, important step in the treatment of pediatric GERD is parental guidance and education. Feeding thickeners, positioning advices and behavioral changes may relieve symptoms in a subset of patients.11,12 There is an on-going debate about drug prescription in treating GERD in infants and children. A recent systematic review by Van der Pol and colleagues concluded that the most commonly prescribed drugs - proton-pump-inhibitors (PPI’s) - are ineffective in reducing GERD-symptoms in infants and evidence is insufficient to support effectiveness and safety of PPI’s in children.13 There is a need for development of new therapeutic strategies for pediatric GERD, but this awaits further elucidation of the pathophysiological mechanisms behind symptoms of GERD in infants and children, such as genes causing or predisposing for GERD.

Infantile hypertrophic pyloric stenosis

Infantile hypertrophic pyloric stenosis (IHPS) is a common gastrointestinal motility disorder of infancy in which an acquired narrowing of the pyloric muscle progressively leads to a nearly obstruction of the pyloric channel.14 Symptoms typically arise in a formerly healthy
infant between the third and sixth week after birth. Projectile postprandial vomiting is typically a key symptom of IHPS.\textsuperscript{15} Although the estimated incidence of IHPS is high among neonates (2/\texttimes 1.000 live births in the Western World), its etiology is still largely unknown.\textsuperscript{15,16} IHPS has a striking male predominance with a male-female ratio of 4-5:1.\textsuperscript{17} Frequently, a palpable mass in the upper abdomen is present and a peristaltic wave can be observed during feeding. Laboratory studies and ultrasound examination may help confirming the clinical diagnosis.

Pyloromyotomy is the only definite treatment of IHPS. The (laparoscopic) pyloromyotomy is a relatively safe procedure, provided a metabolic alkalosis is corrected, and consists of an incision in the circular, hypertrophic pyloric muscle in line with the gut, as first described by Ramstedt in 1912.\textsuperscript{18,19} Conservative management, which consists of prolonged continuous nasoduodenal feeding, is rarely considered and only if a surgical approach seems unfeasible.

**Functional defecation disorders**

Functional defecation disorders (FDD), functional constipation (FC) and functional non-retentive fecal incontinence (FNRFI), are common problems in children. The world-wide prevalence of functional constipation (FC) in children ranges from 0.7 to 29.6 %.\textsuperscript{20} Fecal impaction may lead to fecal incontinence which can be a source of considerable distress and embarrassment for the child and the family. In a subset of children, fecal incontinence occurs without signs of fecal retention, better known as ‘functional non-retentive fecal incontinence’ (FNRFI).\textsuperscript{21} FNRFI has a reported prevalence of 1.5 to 9.8% in children.\textsuperscript{22} Only in a small fraction of patients, a defecation disorder is secondary to a known pathology such as anorectal malformations, Hirschsprung disease, neurological abnormalities or a metabolic disorder.\textsuperscript{23} In the majority of patients however, the etiology remains unknown and a diagnosis of functional defecation disorder is made according to the internationally accepted ROME III criteria for pediatric functional gastrointestinal disorders.\textsuperscript{21} Psycho-education, strict toilet training and keeping bowel diaries combined with a rewarding system are key elements in the treatment of both FC and FNRFI. In addition, FC is generally treated with laxatives, enemas or colon lavage. In case of FNRFI, the use of Loperamide might be beneficial.\textsuperscript{24}

Despite maximal appliance of current conservative treatment modalities, long term follow-up data show that symptoms of FC persist into adulthood in 25% of children, negatively affecting quality of life.\textsuperscript{25} A long-term follow-up study in children with FNRFI demonstrated that 70% of patients still had complaints after two years of intensive treatment. At the age of 12 years, almost 50% of FNRFI patients still suffered from fecal incontinence.\textsuperscript{26} These data demonstrate that there is a need for new treatment strategies for children with FDD. Better insight in the pathophysiology of FDD might be helpful in the development of new treatment modalities, as for now, little is known about the exact etiology of FDD.
The pathophysiology of pediatric gastrointestinal motility disorders

In the last decades, our knowledge about diagnostic techniques in gastrointestinal motility disorders has increased remarkably. However, the pathophysiology behind childhood motility disorders has remained largely hidden. Obtaining more insight in the pathophysiology of gastrointestinal motility disorders will be useful as it will lead to better understanding of these complex diseases and may potentially lead to enhanced therapeutic strategies. Genetic factors, environmental and behavioral factors are all likely to be involved in the complex pathophysiology of gastrointestinal motility disorders in children.

Genetic factors

It is rapidly becoming clear that genetic factors play a role in common disorders such as diabetes mellitus, hypertension and most forms of cancer. It is likely that genetic factors play an important role in the etiology of gastrointestinal motility disorders as well. This becomes already evident when considering results of classical genetics studies: twin studies and familial aggregation studies have shown that several isolated (non-syndromic) motility disorders occur more frequently in relatives of affected persons compared to family members of healthy controls. Furthermore, childhood motility disorders are frequently part of the clinical spectrum of well-defined genetic syndromes. Various studies have been conducted in order to detect the molecular background of isolated motility disorders resulting in only a limited number of genes and their function. A major problem in the identification of these genes is beyond doubt the large genetic heterogeneity of gastrointestinal motility disorders: variations in many different genes can cause the same disease. Still, it will be extremely useful if genes causing gastrointestinal motility disorders and their functions will be detected. It will offer us insight in the complex pathophysiology of gastrointestinal motility disorders, and potentially will lead to new therapeutic strategies.

The field of molecular genetic research is evolving rapidly, which is leading to new, promising and cost-effective techniques that will help identifying the genetic causes of not only Mendelian disorders but also of diseases with a complex origin.

Below, we describe some of the available techniques that are likely to be instrumental in unravelling the genetic pathophysiology of gastrointestinal motility disorders in childhood.

Direct candidate gene sequencing

One strategy starts by studying the function(s) of genes that are already known to cause a particular disorder. Almost without exception proteins (which are coded by genes) do not function in an isolated way but function together with a group of other proteins in a pathway. If one gene in such a pathway can cause a disorder, it may well be possible that mutations in other genes in the same pathway can cause the same disorder, or at least cause a disorder that resembles it. It is essential that the patients that are studied are
phenotyped in such a way they form groups as homogeneous as possible as this strongly increases the chance of finding causative genes. A well-known example of this is the MAPK pathway: first mutations in the gene \textit{PTPN11} were found to cause Noonan syndrome, and by candidate gene sequencing techniques a series of mutations were found in genes acting in the same pathway and causing either also Noonan syndrome or related entities such as Costello syndrome, CFC syndrome and LEOPARD syndrome.\textsuperscript{33}

The increasing knowledge of gene functioning and gene interaction will presumably lead to more successful direct gene sequencing research in gastrointestinal motility disorders in the future.

**Investigating syndromic motility disorders**

Another strategy to detect genes and pathophysiological pathways of isolated motility disorders is to study genes causing syndromic forms. One can recognize patients with the same disorder by the various, ‘non-motility’ manifestations of the syndrome and in this way gather groups of patients with the same cause of the motility disturbance. By studying the functions and associated pathways of genes involved in genetic syndromes with disturbed gut motility, more insight in complex pathophysiology can be obtained. As there are many different syndromic forms of motility disorders, the chance that a single gene or pathway will explain a large part of the group of patients with isolated motility disorder is small. The main yield of this strategy however is the valuable insight it provides in the various pathways leading to abnormal gastrointestinal motility.

**Genome wide association studies**

In Genome Wide Association Studies (GWAS), numerous markers spread throughout the whole genome are used to identify common small variants called single nucleotide polymorphisms (SNPs) in large groups of non-related patients with a particular disorder. SNPs that occur more frequently within the studied population than in a group of healthy controls may indicate a genetic risk factor for the disorder under study. Examples of large GWAS’s are studies performed in groups of patients with hypertension, diabetes, psoriasis or psychiatric disorders. To our knowledge, GWAS studies in gastrointestinal motility disorders have only been performed in a group of patients with Hirschsprung disease and in a cohort of patients with IHPS.\textsuperscript{34,35}

The genome wide association strategy is expensive as it requires large sample sizes to enable detection of significant differences between the affected and control population. Furthermore, most risk factors identified by GWAS’s account only for small proportions of the total genetic risk in complex diseases, due to marked genetic heterogeneity that characterizes many multifactorial disorders. Insufficiently large sample sizes and too low marker densities have been pointed out as factors causing problems in identifying genetic factors associated with complex diseases.\textsuperscript{36} Lastly, GWAS only yields risk factors and not
causative genes: a risk factor may show an association with the disorder in an indirect way. Due to all these problems the number of GWAS’s is decreasing rapidly as more powerful, direct and cheap techniques have become available.

**Linkage studies**

Linkage studies using markers spread over the whole genome and performed in large families with multiple affected members have a strong potential to identify loci at which disease causing genes are located.\(^3\) In linkage analysis, a prior hypothesis or a candidate region is not obliged as the segregation of genetic markers within a pedigree is studied by using microsatellites or single nucleotide polymorphisms (SNP’s) evenly distributed throughout the genome. Possibly associated chromosomal regions identified in this way need to be sequenced further by traditional Sanger sequencing or next generation sequencing (see **Whole exome sequencing**). Many genes for many entities have been found this way. For example, in 2006, a genome wide linkage analysis was performed in five affected and six non-affected members of one multigenerational family with isolated Hirschsprung disease.\(^3\) In this way, a novel susceptibility locus on chromosome 4q was identified for Hirschsprung disease. Up till now, at least ten genes and 5 loci have been found to be associated with isolated Hirschsprung disease, which underlines the clinical heterogeneity of this entity.\(^3\)

It can be expected that linkage analysis in homogeneous isolated motility disorders in well-defined families will lead to the identification of disease associated genes. Subsequently, isolated genes can be checked in large series of unrelated patients to evaluate whether it is a common or rare explanation for the disturbed motility.

**Whole exome sequencing**

Recently, a new genetic technique called whole exome sequencing (WES) using next generation sequencing techniques has become available. This technique focuses on just the exons, so the protein-coding parts of the genome, covering approximately 1% of the total genome. This decreases the work of sequencing dramatically, and especially the work attached to the bio-informatics thereafter. Sequencing all exons of the human genome (usually indicated as the exome), has proven to be robust, also for disorders with a presumably heterogenic background. In 2010, WES in just four affected individuals with a single, well defined entity was successful in identifying a disease associated gene.\(^4\) From then, the genetic background of several complex disorders, such as the vast number of causes for autism spectrum disorders, has been further elucidated by WES each time using only small numbers of patients.\(^4\)\(^,\)\(^5\)

Which of the abovementioned techniques to apply in individual research projects largely depends on the degree of clinical homogeneity of the study population and to some extent
the available sample size. Detailed phenotyping of study populations remains a hallmark for successful genetic research.\textsuperscript{43}

Environmental factors
Next to the presence of certain variants within the genome (the genetic make-up of individuals), environmental factors, such as nutrition, climate, cultural habits and exposure to certain agents, might also play a role in the etiology of gastrointestinal motility disorders. Next to the direct influences on health that these factors may have, they may also influence our genome possibly leading to motility disorders. Our DNA is subject to continuous changes induced by such environmental factors that result in changes in imprinting status by shifts in methylation and thereby gene expression, which can be inherited over several generations.\textsuperscript{44} These factors may act anywhere between the moment of conception and postnatal life. It may be either completely environmentally determined factors, or environmentally determined factors that act mainly in the presence of a particular genetic constitution. Epigenetic changes should therefore also be considered when investigating the pathophysiology of pediatric gastrointestinal motility disorders.

Associated behaviors
The association between behavioral factors and FDD has been increasingly acknowledged but the exact relationship between the two is still unclear. In more than one-third of children with an FDD, behavioral problems can be found.\textsuperscript{45-47} Up till now it has remained uncertain whether behavioral disturbances in general are primary or secondary to FDD. It can be hypothesized that pre-existing behavioral disturbances may lead to a complicated period of toilet training, which is known as a possibly critical phase in the development of FDD.\textsuperscript{53} On the other hand, the presence of an FDD might give rise to a considerable level of stress and embarrassment for the child and his/her family which may lead to adaptive behavioral changes. These behavioral changes might also become apparent in the parents of children with FDD. Little is known about the health status, personality and child rearing style of parents of children with FDD.

Remarkably, in children with autism spectrum disorders, the prevalence of FDD has frequently been reported to be much higher than in the general population.\textsuperscript{48-52} However, no data is available about the prevalence of autism spectrum disorders in children presenting with FDD. Obtaining more insight in FDD associated behaviors in both children and parents might give rise to an adaptation of the current treatment strategies and might lead to a more systemic family-based approach when treating children with FDD.
Outline of the thesis

This thesis focuses on the further elucidation of the pathophysiology of the three most common gastrointestinal motility disorders in children; gastro-esophageal reflux disease, infantile hypertrophic pyloric stenosis and functional defecation disorders. Genetic factors, environmental factors and associated behaviors have been studied in order to increase our insight in these conditions.

Part I; Gastro-esophageal reflux disease (GERD)

In Chapter 1 a large multigenerational Dutch family with multiple members affected with GERD is described. Detailed phenotyping of the family members was performed and subsequently genome-wide linkage analysis was conducted in order to identify genetic loci associated with GERD in this family.

Part II; Infantile hypertrophic pyloric stenosis (IHPS)

An extensive overview of the current knowledge of the pathophysiology of IHPS is provided in Chapter 2. Genetic studies that have been performed in isolated forms of IHPS are discussed. Furthermore, a detailed overview of all non-isolated (syndromic) forms of IHPS is given. Pathophysiological pathways known to be associated with these extreme phenotypes are further categorized in order to obtain new insights in to the pathophysiology of isolated IHPS.

Studies that have been published regarding possible seasonal variations in the incidence of IHPS have been contradictory and local environmental factors have generally not been taken in to account. In Chapter 3, seasonal variations in the incidence of IHPS are investigated in two separate regions in the Netherlands correcting for local climate factors.

Part III; Functional defecation disorders (FDD)

Chapter 4 comprises an overview of the current knowledge of genetic factors associated with childhood constipation. In this chapter, we discuss genetic studies conducted in isolated forms of childhood constipation. Subsequently, we provide an overview of clinical syndromes known to be associated with childhood constipation (syndromic forms). These non-isolated forms of childhood constipation are further subcategorized according to their presumed pathogenesis in order to provide better insight in to the possible pathophysiological pathways associated with isolated forms of childhood constipation.

In children with autism spectrum disorders, FDD have been commonly described. However, no data has been published about the prevalence of (symptoms of) autism spectrum disorders in children presenting with FDD. In Chapter 5, the prevalence of symptoms
of autism spectrum disorders is prospectively and systematically assessed in children presenting with an FDD at our specialized outpatient clinic.

The presence of a functional defecation disorder (FDD) may delay the moment of completion of toilet training. However, the association between the presence of symptoms of autism spectrum disorders and the moment of completion of toilet training in patients with FDD is unknown. In Chapter 6, we compare the moment of completion of toilet training between children with FDD and symptoms of autism spectrum disorders with children with an FDD only and controls from the general population.

In mothers of children with chronic abdominal pain, anxiety and depression have been found to be more commonly present compared to mothers of healthy children. No such data are available for the parents of children with FDD. More knowledge about this subject might improve our insight in the etiology of FDD in children and might teach us about the possible influences that the presence of an FDD in a child might have on parents. Health status, personality and child rearing style of fathers and mothers of children with FDD are described in Chapter 7.

We conclude with Chapter 8, where we describe the efficacy of a new therapeutic option in a subgroup of patients with a very specific constipation phenotype. In this chapter, the results of sacral neuromodulation therapy are demonstrated in a specific subgroup of female adolescent patients with severe refractory functional constipation.
Reference List


