26 Motility Problems in Developmental Disorders: Cerebral Palsy, Down Syndrome, Williams Syndrome, Autism, Turner's Syndrome, Noonan's Syndrome, Rett Syndrome, and Prader-Willi Syndrome

Massimo Martinelli and Annamaria Staiano

Cerebral Palsy

Cerebral palsy (CP) refers to a group of chronic, nonprogressive disorders of movement, posture, and tone due to central nervous system (CNS) damage occurring before cerebral development is complete. The prevalence of CP is approximately 2/1000 live births. The different types of CP vary from series to series, with the spastic type being the most frequent, while periventricular leukomalacia and/or cortical/cerebral atrophy represents the main neuropathological correlates [1]. The survival of children with severe neurological disorders, such as cerebral palsy, has created a major challenge for medical care. Gastrointestinal (GI) motor dysfunction, such as gastroesophageal reflux disease (GERD), dysphagia, vomiting, and chronic constipation, is known to occur frequently in children with different degrees of CNS damage. The degree of GI dysmotility seems to correlate with the degree of brain damage [2]. Swallowing disorders are common in patients affected by CP. In a study by Del Giudice and colleagues, the authors found that 30 of 35 patients with CP presenting with dysphagia had swallowing disorders. The majority of patients showed dysfunction of the oral phase of swallowing with abnormal formation of the alimentary bolus, due to either uncoordinated movements of the tongue or it being contracted and rigid. Alternatively, they had a normal bolus but substantial defects in its propulsion toward the oropharynx, due to the lack of finely coordinated movements of the tongue against the palate. Swallowing disorders have significant implications for development, nutrition, respiratory health, and GI function of this group of patients [3]. The development of dysphagia is associated with a progressive reduction of food intake and represents the main pathogenic factor for malnutrition [4]. Swallowing disorders can also cause recurrent episodes of pulmonary aspiration. For all these reasons, it is essential to diagnose these conditions as early as possible. Videofluoroscopic swallow studies are considered to be a valuable diagnostic tool for children with CP, given their ability to assess both pharyngeal motility and airway protection during swallowing. There is growing evidence that the method of feeding is an important variable in outcomes of children with more severe CP. In those patients with dysphagia, undernutrition, and associated respiratory diseases, the implementation of gastrostomy tube feeding is recommended [5–7]. The American Academy of Cerebral Palsy and Developmental Medicine considers gastrostomy feeding as a valuable alternative nutritional source in this group of children [6]. GERD is very common in patients with a severe neurologic impairment. The prevalence is reported to be between 70 and 90 %, depending upon the different investigations used, including esophageal pH studies and/or upper GI endoscopy [3, 8]. The pathogenesis of GERD in children with CP seems to relate mainly to the impaired motility of the esophagus. Del Giudice et al. demonstrated that most of the patients with neurological handicaps affected by GERD showed prolonged gastric emptying and abnormal esophageal motility. The main abnormalities consisted of significantly lower than normal amplitude of the lower esophageal sphincter (LES) and esophageal peristalsis and an increased number of simultaneous waves, compared to control children (Fig. 26.1) [3]. These findings, part of a more generalized dysmotility of the GI tract, together with other predisposing factors often present in these children, such as spasticity, prolonged supine position, scoliosis, seizures, and reduced amounts of swallowed saliva consequent to drooling, increase the predisposition to the development of GERD and may be responsible for a high failure rate of both medical and surgical treatments. The ideal therapeutical approach to GERD in CP patients is still controversial. According to

M. Martinelli, M.D. • A. Staiano, M.D. (✉)
Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II" Italy, via Pansini 5, Naples 80131, Italy
e-mail: martinellimassimo@hotmail.com; staiano@unina.it

C. Faure et al. (eds.), *Pediatric Neurogastroenterology*, DOI 10.1007/978-3-319-43268-7_26

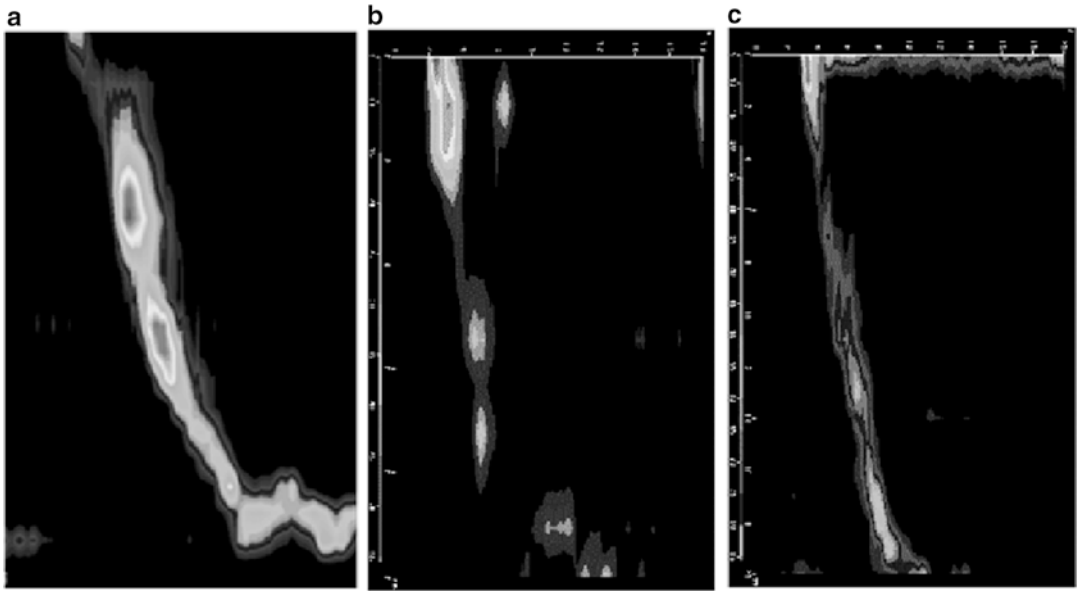

Fig. 26.1 Examples of high-resolution esophageal manometry tracings in a control subject (**a**) and in two patients (**b**, **c**) affected by cerebral palsy. Note in (**a**) a normal esophageal tracing, whereas in (**b**) hypotensive lower esophageal sphincter and low amplitude contraction. In (**c**), marked hypomotility of the smooth muscle region is recognizable

the recent guidelines from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN–NASPGHAN) on gastroesophageal reflux, antisecretory therapy should be optimized. Long-term treatment with proton pump inhibitors (PPIs) is often effective for symptom control and maintenance of remission. Baclofen may be used to control vomiting [9]. An alternative medical approach is represented by the use of an elemental diet. We described a lower incidence of GERD in neurologically impaired children with refractory esophagitis treated with amino acid-based formula [10]. However, conventional medical management is less effective in neurologically impaired children. At the same time, surgical intervention is associated with high operative risk given the often suboptimal physical condition of the patients. The benefit/risk ratio of antireflux surgery in patients with persistent symptoms despite optimized medical therapy is not clear. The Nissen fundoplication has been associated with several complications in neurologically impaired children. Postoperative morbidity rates are up to 50 %, reoperation rates up to 20 %, and mortality is substantial [11, 12]. Recently, the advent of laparoscopic Nissen fundoplication has become the procedure of choice. Esposito and colleagues reported a 30 % rate of postoperative complications and 6 % rate of reoperation [13].

Constipation represents another frequent and often undiagnosed problem in patients with CP. The prevalence of the chronic constipation varies from 25 to 75 % in patients with CP [3]. Chronic constipation is often the result of prolonged colonic transit, which is secondary to the underlying gut dysmotility. Colonic transit time seems to be delayed predominantly in the left colon and rectum [14]. It has been suggested that disruption of the neural modulation of colonic motility may play an important role in the development of constipation in children with neurologic diseases. The low fiber and fluid intake and the frequent delay in diagnosis certainly contribute to the development and the persistence of constipation in neurologically impaired children. Staiano et al. demonstrated the efficacy of dietary fiber glucomannan in improving bowel frequency in children with severe brain damage, despite no measurable effects on delayed colonic transit [15].

Down Syndrome

About 77 % of neonates affected by Down syndrome (DS) present with or develop GI abnormalities [16]. Cleves et al., in a recent cohort study, showed an elevated relative risk for GI malformations (OR 67.07) in infants with DS [17]. The most frequent GI malformation associated with DS is Hirschsprung disease; however, esophageal atresia, tracheoesophageal fistula, duodenal atresia or stenosis, and imperforate anus are all well-described associations. Some of the most commonly GI symptoms reported by patients with DS are dysphagia for liquids and solids, vomiting/GER, and heartburn, as well as other esophageal dysmotility symptoms [18]. Children affected by DS are at high risk of GERD [19] and its serious complications such as oropharyngeal aspira-

tion and pneumonia. Much like in other conditions with neurological impairment such as CP, treatment of GERD in DS should combine optimization of antisecretory therapy and behavioral interventions including feeding and positional changes. Despite correct and aggressive medical therapy, some patients with DS, especially patients with respiratory complications of GERD, need antireflux surgery [20]. It has been observed that neurological impairment and GI disease necessitating surgery are independently associated with poorer developmental outcome [21]. In regard to esophageal motor disorders, different cases of association between achalasia and DS have been described, and although achalasia remains a rare entity, it should be considered in any patient with DS who presents with dysphagia [22]. Severe chronic constipation is also highly prevalent [23]. In children with chronic constipation, it is important to exclude Hirschsprung disease (HSCR), observed in approximately 1 out of 200–300 patients with DS [24]. About 30 % of HSCR patients have a recognized chromosomal abnormality, a recognized syndrome, or additional congenital anomalies, the most frequent of which being indeed DS [25]. Moore et al., studying a population of 408 HSCR patients, reported a prevalence of 3.2 % of DS [26], suggesting a possible role for chromosome 21 in the etiology of HD. Nevertheless, the existence of trisomy 21 although seemingly increasing the risk of developing HSCR does not invariably lead to its occurrence. Several studies investigating the role of chromosome 21 as a potential candidate area for a modifying gene in HSCR exist [27], but in the last few years, the possible role of genes mapping outside chromosome 21 (such as SOD1, ITGB2, protein s-100 beta) is emerging. Also, well studied has been the relationship between the major susceptibility genes associated with HSCR (RET and EDNRB) and DS. Arnold et al. [28] demonstrated that the RET enhancer polymorphism RET 19.7 at chromosome 10q11.2 is associated with HSCR in individuals with DS. Interestingly, the RET19.7T allele frequency is significantly different between individuals with DS alone (0.26 ± 0.04), HSCR alone (0.61 ± 0.04), and HSCR and DS (0.41 ± 0.04), demonstrating an association and interaction between RET and chromosome 21 gene dosage. Similarly, a novel EDNRB variant was identified in DS patients with HSCR [29]. There appears to be a significantly higher overall incidence of both pre- and postoperative enterocolitis in DS with HSCR [30].

Williams Syndrome

Williams syndrome (WS), also known as Williams-Beuren syndrome, is due to a homozygous deletion of a contiguous gene on the long arm of chromosome 7 (7q11.23) [31]. The estimated prevalence of WS is 1 in 7500 live births [32]. Most individuals with WS (99 %) have a 1.5 megabase deletion in 7q11.23 encompassing the elastin gene (ELN) and 25–35 other genes, all of which are detectable by fluorescent in situ hybridization (FISH) [33]. Clinical features of WS include distinctive facial anomalies; congenital heart defects, in particular supravalvular aortic stenosis; slight to severe mental retardation; hernia; growth deficiency; and infantile hypercalcemia [34]. Gastrointestinal symptoms such as chronic abdominal pain, feeding problems, constipation, and GERD are seen relatively frequently in children with WS [35]. Hypercalcemia may contribute to irritability, vomiting, constipation, and muscle cramps; it is more common in infancy but may recur in adults [36].

Autism

Autism spectrum disorder (ASD) is a neurodevelopmental condition that unfolds in the first few years of life and involves severe impairments in social interaction and communication, with restriction in interests and extreme attachment to routine or to repetitive or perseverative behaviors [37]. The term includes autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified [37]. Estimates of ASD in pediatric populations have dramatically increased over the past decade, with ~1 in every 88 children meeting diagnostic criteria in the United States [38]. GI dysfunction is frequently reported among children with ASD, and many causal and therapeutic theories of ASD involve the GI system [39]. This includes the hypothesis that a specific GI pathology is associated with ASD, triggered by abnormal immune function or elevated intestinal permeability. A great amount of controversy has surrounded this issue since a publication in 1998 naming a new pathologic entity, "autistic enterocolitis," as responsible for developmental regression in 12 children after administration of the measles-mumps-rubella (MMR) vaccine [40]. Ultimately, this research was retracted for several reasons, including questionable research practices, as found by the General Medical Council of the United Kingdom [41]. Although the presence of a unique GI pathophysiology specific to ASDs has yet to be identified, elevated risk for GI symptoms in this population remains a critical issue in pediatric settings, because this population is significantly more likely to use GI agents and experience hospitalizations related to GI disturbances. The prevalence of GI symptoms in children with ASDs is poorly understood, and it is still unclear whether it is increased when compared with control subjects. Indeed, prospective well-controlled studies are unavailable. To date, prevalence has been reported with a wide range from 9 to 70 % [42–44]. A recent meta-analysis investigating GI symptoms among children with ASD concluded that ASD patients experience significantly more general GI symptoms than comparison groups (mean difference: 0.82, OR: 4.42) [45]. The most common GI symptoms

reported in children with ASDs are chronic constipation, abdominal pain with or without diarrhea, and encopresis as a consequence of constipation [39]. Other gastrointestinal motility abnormalities that have been described for individuals with ASDs include GERD and abdominal bloating [39]. In children with ASDs, gastrointestinal conditions can present typically or atypically as non-gastrointestinal manifestations, including behavioral changes. Horvath et al. reported disturbed sleep and nighttime awakening in 52 % of children with ASDs who had gastrointestinal symptoms (vs 7 % of age-matched healthy sibling) [42]. Children with ASDs who had reflux esophagitis exhibited unexplained irritability more frequently (43 %) than those who did not (13 %) [42]. Behavioral changes may be markers of abdominal pain or discomfort in individuals with ASDs [46]. Nevertheless, a consensus report on the evaluation, diagnosis, and treatment of GI disorders in individuals with ASDs published in 2010 concluded that the existence of a gastrointestinal disturbance specifically correlated with ASDs has not been established [39]. Well-designed trials are therefore needed in order to develop evidence-based recommendations for optimal diagnostic and treatment strategies in children with ASDs. Until then, current consensus is that application and, when necessary, adaptation of conventional recommendations for the general pediatric population are also relevant to children with ASDs [39].

Turner's Syndrome

Turner's syndrome (TS) affects about 1 in 2000 live births females [47]. In about 50 % of cases, karyotype analysis of peripheral lymphocytes reveals the complete loss of one X chromosome (karyotype 45,X) whereas the remaining patients display a multitude of chromosomal abnormalities, including part absence of one X chromosome or mosaicism [47]. In the early 1980s, Chen et al. reported a high incidence of feeding difficulties in early childhood in children affected by TS, associated with regurgitation and vomiting [48]. In 1992, Mathisen and colleagues investigated 10 infants affected by TS and 10 control girls in order to detect oral-motor dysfunction and feeding disorders [49]. Through the use of video recording of routine meals and the administration of the Feeding Assessment Schedule (FAS), the authors clearly demonstrated that patients affected by TS presented considerable and persistent early feeding problems correlated with a characteristic range of oral-motor dysfunctions [49]. Breast-feeding as well as introduction of solid foods was especially difficult for the mothers of case infants. In addition, most of the case-group mothers reported vomiting and regurgitation, suggesting that some children with Turner's syndrome may have some dysfunction of the lower gastroesophageal tract [49]. Following these findings, Staiano and colleagues evaluated upper gastrointestinal motility in patients with Turner's syndrome in order to detect the presence of GI motor dysfunctions [50]. The study population consisted of 13 girls with TS and two comparison groups: seven girls with familial short stature and eight control girls. All the subjects underwent a scintigraphic gastric emptying study. In addition, six girls with TS and eight control children also underwent esophageal manometry [50]. The percentage of retention of solids at 60 and 90 min was significantly greater in patients with TS than in control subjects and in children with familial short stature. Five of the 13 girls with Turner's syndrome had a gastric emptying at 60 min exceeding the mean plus 2 standard deviations of the results in control children. Conversely, esophageal manometry did not show significant differences in TS children when compared with controls group. The authors concluded that the impaired gastric motility represented a novel gastrointestinal finding of this syndrome. To the best of our knowledge, no further report of motility dysfunction in TS children has successively been published.

Noonan's Syndrome

Noonan's syndrome (NS) is an autosomal dominant disorder characterized by short stature, typical face dysmorphology, and congenital heart defects. The incidence of NS is reported to be between 1 in 1000 and 1 in 2500 live births [51]. Severe feeding difficulties are commonly described in children with NS, although the prevalence and underlying cause are poorly understood [52]. In 1992, Sharland and colleagues reported the clinical characteristics of 151 children affected by NS. Feeding histories were obtained in 144 children. Significant feeding difficulties were reported in 75 % of children [52]. In 24 % of these patients, these difficulties were defined as severe, requiring tube feeding for 2 weeks or longer. In 38 % of cases, feeding difficulties were moderate, defined as very poor suck, with slow feeding and recurrent vomiting [52]. Following these early reports, in 1999 Shah et al. conducted a study in order to characterize gastrointestinal motility in children affected by NS [53]. Twenty-five children with NS were consecutively enrolled. Poor feeding described as poor suck or refusal to drink or eat solids, and recurrent vomiting were present in 16 patients. Eight of 16 infants with gastrointestinal symptoms had evidence of gastroesophageal reflux [53]. The children with the most severe symptoms were further investigated by surface electrogastrography (EGG) and antroduodenal manometry (ADM). Four of the five patients who underwent EGG had evidence of abnormal gastric myoelectrical activity. ADM showed an immature contractile activity rather than neuropathological in appearance, reminiscent of that seen in neonates of 32–35 weeks' gestation [53].

Rett Syndrome

Rett syndrome is a neurodevelopmental disorder characterized by a period of developmental regression at approximately 6–18 months with loss of hand and communication skills, development of hand stereotypies, and impaired gait [54]. Most cases are caused by a mutation in the MECP2 gene [54]. As with other neurodevelopmental conditions, disorders of GI motility such as GERD, constipation, and abdominal bloating are common [55]. Recently, a group of experts published a systematic review of the literature in order to provide some practical recommendations for the management of GI motility disorders in children with Rett syndrome [56]. GERD has been reported up to 39 % of girls and women affected by Rett syndrome [57]. According to the experts' panel, common presenting symptoms include vomiting, rumination, regurgitation, and respiratory signs, and unexplained weight loss [56]. The diagnostic approach should not differ from other patients with GERD, including pH-monitoring and upper GI endoscopy. Regarding the treatment, the majority of the panel agreed that conservative strategies such as small frequent feeds and the use of more upright positions in combination with pharmacological management should be adopted [56]. Laparoscopic fundoplication should only be advised in case of refractory GERD. Despite the frequency reported to be up to 80 % of girls and women in a recent US family survey [57], there remains a paucity of evidence as to how constipation should be best diagnosed and treated. Diagnosis is often difficult due to the communication challenges. A stepwise plan for management was identified with a high rate of agreement from the panel members on the use of various laxative agents [56]. Abdominal bloating, as a result of aerophagia, has been reported in almost half of the cases in a population-based sample [58]. In some case reports, severe aerophagia has been associated with gastric perforation [59]. Use of simethicone or magnesium sulfate or selective serotonin reuptake inhibitors has been suggested. There was no consensus on the use of magnesium sulfate; its use has only been supported by case reports. Where symptoms are severe, a gastrostomy may be considered [56].

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a multisystemic genetic disease which was first described in 1956 [60]. The incidence of PWS is 1:15,000–30,000 newborns. The syndrome is characterized by muscular hypotonia, feeding difficulties, failure to thrive, developmental delay, short stature, and hypogonadism [60]. Gastrointestinal motility in children with PWS has been sparsely investigated. Following case reports describing gastric rupture in PWS children [61, 62], Arentz and colleagues measured the gastric emptying in eight pediatric patients with PWS through nucleotide scintigraphy after a standardized test meal [63]. In contrast with adult literature [64], the authors found a delayed emptying in 5 out of 8 children and concluded that this may represent a risk factor for the development of gastric rupture [63]. More recently, Kuhlmann et al. evaluated colorectal function in 21 adult patients with PWS [65]. All enrolled patients underwent a whole assessment for diagnosis of constipation including total gastrointestinal transit time (GITT). Eight out of 21 patients fulfilled diagnostic criteria for functional constipation, and GITT was >3 days in 24 % of PWS and none of the controls. To the best of our knowledge, no pediatric study has evaluated the prevalence of functional constipation among PWS children.

References

1. Kuban KC, Leviton A. Cerebral palsy. N Engl J Med. 1994;330:188–95.
2. Staiano A, Cucchiara S, Del Giudice E, Andreotti MR, Minella R. Disorders of oesophageal motility in children with psychomotor retardation and gastro-oesophageal reflux. Eur J Pediatr. 1991; 150:638–41.
3. Del Giudice E, Staiano A, Capano G, et al. Gastrointestinal manifestations in children with cerebral palsy. Brain Dev. 1999;21:307–11.
4. Campanozzi A, Capano G, Miele E, et al. Impact of malnutrition on gastrointestinal disorders and gross motor abilities in children with cerebral palsy. Brain Dev. 2007;29:25–9.
5. Schwarz SM, Corredor J, Fisher-Medina J, Cohen J, Rabinowitz S. Diagnosis and treatment of feeding disorders in children with developmental disabilities. Pediatrics. 2001;108:671–6.
6. Samson-Fang L, Butler C, O'Donnell M, AACPDM. Effects of gastrostomy feeding in children with cerebral palsy: an AACPDM evidence report. Dev Med Child Neurol. 2003;45:415–26.
7. Sullivan PB, Juszczak E, Bachlet AM, et al. Gastrostomy tube feeding in children with cerebral palsy: a prospective, longitudinal study. Dev Med Child Neurol. 2005;47:77–85.
8. Wesley JR, Coran AG, Sarahan TM, Klein MD, White SJ. The need for evaluation of gastroesophageal reflux in brain-damaged children referred for feeding gastrostomy. J Pediatr Surg. 1981;16: 866–71.
9. Vandenplas Y, Rudolph CD, Di Lorenzo C et al. North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009; 49:498–547.
10. Miele E, Staiano A, Tozzi A, Auricchio R, Paparo F, Troncone R. Clinical response to amino acid-based formula in neurologically impaired children with refractory esophagitis. J Pediatr Gastroenterol Nutr. 2002;35:314–9.
11. Richards CA, Andrews PL, Spitz L, Milla PJ. Nissen fundoplication may induce gastric myoelectrical disturbance in children. J Pediatr Surg. 1998;33:1801–5.
12. Richards CA, Carr D, Spitz L, Milla PJ, Andrews PL. Nissen-type fundoplication and its effects on the emetic reflex and gastric motility in the ferret. Neurogastroenterol Motil. 2000;12:65–74.

13. Esposito C, Van Der Zee DC, Settimi A, Doldo P, Staiano A, Bax NM. Risks and benefits of surgical management of gastro-esophageal reflux in neurologically impaired children. Surg Endosc. 2003;17:708–10.
14. Staiano A, Del Giudice E. Colonic transit and anorectal manometry in children with severe brain damage. Pediatrics. 1994;94:169–73.
15. Staiano A, Simeone D, Del Giudice E, Miele E, Tozzi A, Toraldo C. Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. J Pediatr. 2000;136:41–5.
16. Spahis JK, Wilson GN. Down syndrome: perinatal complications and counseling experiences in 216 patients. Am J Med Genet. 1999;89:96–9.
17. Cleves MA, Hobbs CA, Cleves PA, Tilford JM, Bird TM, Robbins JM. Congenital defects among liveborn infants with Down syndrome. Birth Defects Res A Clin Mol Teratol. 2007;79:657–63.
18. Zarate N, Mearin F, Hidalgo A, Malagelada J. Prospective evaluation of esophageal motor dysfunction in Down's syndrome. Am J Gastroenterol. 2001;96:1718–24.
19. Buchin PJ, Levy JS, Schullinger JN. Down syndrome and the gastro-intestinal tract. J Clin Gastroenterol. 1986;8:111–4.
20. Vernon-Roberts A, Sullivan PB. Fundoplication versus post-operative medication for gastro-oesophageal reflux in children with neurological impairment undergoing gastrostomy. Cochrane Database Syst Rev. 2007;(1):CD006151.
21. van Trotsenburg AS, Heymans HS, Tijssen JG, de Vijlder JJ, Vulsma T. Comorbidity, hospitalization, and medication use and their influence on mental and motor development of young infants with Down syndrome. Pediatrics. 2006;118:1633–9.
22. Okawada M, Okazaki T, Yamataka A, Lane GJ, Miyano T. Down's syndrome and esophageal achalasia: a rare but important clinical entity. Pediatr Surg Int. 2005;21:997–1000.
23. Wallace RA. Clinical audit of gastrointestinal conditions occurring among adults with Down syndrome attending a specialist clinic. J Intellect Dev Disabil. 2007;32:45–50.
24. Quinn FM, Surana R, Puri P. The influence of trisomy 21 on outcome in children with Hirschsprung's disease. J Pediatr Surg. 1994;29:781–3.
25. Chakravarti A, Lyonnet S. Hirschsprung disease. In: Scrivner CR, Beaudet AR, Sly W, Valle D, editors. The metabolic and molecular bases of inherited disease. 8th ed. New York: McGraw-Hill; 2001. p. 6231–55.
26. Moore SW. The contribution of associated congenital anomalies in understanding Hirschsprung's disease. Pediatr Surg Int. 2006;22: 305–15.
27. Puffenberger E, Kauffman E, Bolk S, et al. Identity-by-descent and association mapping of a recessive gene for Hirschsprung disease on human chromosome 13q22. Hum Mol Genet. 1994;3:1217–25.
28. Arnold S, Pelet A, Amiel J, et al. Interaction between a chromosome 10 RET enhancer and chromosome 21 in the Down syndrome—Hirschsprung Disease Association. Hum Mutat. 2009;30:771–5.
29. Zaahl MG, du Plessis L, Warnich L, Kotze MJ, Moore SW. Significance of novel endothelin-B receptor gene polymorphisms in Hirschsprung's disease: predominance of a novel variant (561C/T) in patients with co-existing Down's syndrome. Mol Cell Probes. 2003;17:49–54.
30. Morabito A, Lall A, Gull S, Mohee A, Bianchi A. The impact of Down's syndrome on the immediate and long-term outcomes of children with Hirschsprung's disease. Pediatr Surg Int. 2006; 22:179–81.
31. Merla G, Ucla C, Guipponi M, Reymond A. identification of additional transcripts in the Williams-Beuren syndrome critical region. Hum Genet. 2002;110:429–38.
32. Stromme P, Bjornstad PG, Ramstad K. Prevalence estimation of Williams syndrome. J Child Neurol. 2002;17:269–71.
33. Lowery MC, Morris CA, Ewart A, Brothman LJ, Zhu XL, Leonard CO, et al. Strong correlation of elastin deletions, detected by FISH, with Williams syndrome: evaluation of 235 patients. Am J Hum Genet. 1995;57:49–53.
34. Greenberg F. Williams syndrome professional symposium. Am J Med Genet Suppl. 1990;6:85–8.
35. Morris CA, Demsey SA, Leonard CO, Dilts C, Blackburn BL. Natural history of Williams syndrome: physical characteristics. J Pediatr. 1988;113:318–26.
36. Morris CA, Pober V, Wang P, et al. Medical guidelines for Williams syndrome. Williams Syndrome Association Website; 1999.
37. Johnson CP, Myers SM, American Academy of Pediatrics, Council on Children With Disabilities. Identification and evaluation of children with autism spectrum disorders. Pediatrics. 2007;120:1183–215.
38. Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders: autism and developmental disabilities monitoring network, 14 sites, United States, 2008. MMWR Surveill Summ. 2012;61(SS03):1–19. www.cdc.gov/ncbddd/autism/documents/ADDM-2012-Community-Report.pdf.
39. Buie T, Campbell DB, Fuchs III GJ, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics. 2010;125 Suppl 1:S1–18.
40. RETRACTED: Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 1998;351:637–41.
41. Retraction-Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 2010;375(9713):445.
42. Horvath K, Perman JA. Autism and gastrointestinal symptoms. Curr Gastroenterol Rep. 2002;4:251–8.
43. Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. BMJ. 2002;325:419–21.
44. Valicenti-McDermott M, McVicar K, Rapin I, Wershil BK, Cohen H, Shinnar S. Frequency of gastrointestinal symptoms in children with autistic spectrum disorders and association with family history of autoimmune disease. J Dev Behav Pediatr. 2006;27(2 Suppl): S128–36.
45. McElhanon BO, McCracken C, Karpen S, Sharp WG. Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis. Pediatrics. 2014;133:872–83.
46. Carr EG, Owen-DeSchryver JS. Physical illness, pain, and problem behavior in minimally verbal people with developmental disabilities. J Autism Dev Disord. 2007;37:413–24.
47. Ranke MB, Saenger P. Turner's syndrome. Lancet. 2001;358: 309–14.
48. Chen H, Faigessbaum D, Weiss H. Psychosocial aspects of patients with the Ulrich-Turner syndrome. Am J Med Genet. 1981;8: 191–203.
49. Mathisen B, Reilly S, Skuse D. Oral-motor dysfunction and feeding disorders of infants with Turner syndrome. Dev Med Child Neurol. 1992;34:141–9.
50. Staiano A, Salerno M, Di Maio S, et al. Delayed gastric emptying: a novel gastrointestinal finding in Turner's syndrome. Arch Dis Child. 1996;75:440–3.
51. Turner AM. Noonan syndrome. J Paediatr Child Health. 2014;50:E14–20.
52. Sharland M, Burch M, Mckenna WM, Paton MA. A clinical study of Noonan syndrome. Arch Dis Child. 1992;67:178–83.
53. Shah N, Rodriguez M, Louis DS, Lindley K, Milla PJ. Feeding difficulties and foregut dysmotility in Noonan's syndrome. Arch Dis Child. 1999;81:28–31.
54. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010; 68:944–50.

55. Motil KJ, Schultz RJ, Browning K, et al. Oropharyngeal dysfunction and gastroesophageal dysmotility are present in girls and women with Rett syndrome. J Pediatr Gastroenterol Nutr. 1999;29:31–7.
56. Baikie G, Ravikumara M, Downs J, et al. Gastrointestinal dysmotility in Rett syndrome. J Pediatr Gastroenterol Nutr. 2014;58:237–44.
57. Motil KJ, Caeg E, Barrish JO, et al. Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome. J Pediatr Gastroenterol Nutr. 2012;55:292–8.
58. Colvin L, Fyfe S, Leonard S, et al. Describing the phenotype in Rett syndrome using a population database. Arch Dis Child. 2003; 88:38–43.
59. Shah MB, Bittner JGT, Edwards MA. Rett syndrome and gastric perforation. Am Surg. 2008;74:315–7.
60. Cassidy SB, Driscoll DJ. Prader-Willi syndrome. Eur J Hum Genet. 2009;17:3–13.
61. Wharton RH, Wang T, Graeme-Cook F, Briggs S, Cole RE. Acute idiopathic gastric dilation with gastric necrosis in individuals with Prader-Willi syndrome. Am J Med Genet. 1997;73:437–41.
62. Stevenson DA, Heinemann J, Angulo M, et al. Gastric rupture and necrosis in Prader-Willi syndrome. J Pediatr Gastroenterol Nutr. 2007;45:272–4.
63. Arenz T, Schwarzer A, Pfluger T, Koletzko S, Schmidt H. Delayed gastric emptying in patients with Prader Willi syndrome. J Pediatr Endocrinol Metab. 2010;23:867–71.
64. Hoybye C, Barkeling B, Naslund E, Thoren M, Hellstrom PM. Eating behavior and gastric emptying in adults with Prader-Willi syndrome. Ann Nutr Metab. 2007;51:264–9.
65. Kuhlmann L, Joensson IM, Froekjaer JB, Krogh K, Farholt S. A descriptive study of colorectal function in adults with Prader-Willi syndrome: high prevalence of constipation. BMC Gastroenterol. 2014;14:63.