Gastrointestinal Disorders and Autism

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Introduction

Infantile autism was described for the first time by Kanner in 1943. In 1994, the Diagnostic and Statistical Manual of Mental Disorder of the American Psychiatric Association (DSM-IV) used the term pervasive developmental disorders to describe infantile autism and other disorders with common behavioral features. A new edition of the DSM (DSM-5) proposes a revised and definitive terminology, namely autism spectrum disorders (ASDs).

ASDs are conditions characterized by impairment of social interaction and of verbal and nonverbal communication, poor social skills, a limited range of interests, and repetitive behaviors. The ASDs category considers inclusion criteria and other possible clinical features associated with ASDs (American Psychiatric Association 2012). In this chapter, autism and ASDs will be used interchangeably.

Autism is a neurobiological disorder; its etiology is heterogeneous and presents a complex interplay among contributing genetic and environmental factors.

Idiopathic ASDs are distinguished from non-idiopathic/syndromic ASDs. While idiopathic ASDs are cases without genetic, metabolic diseases or cerebral lesions, non-idiopathic/syndromic ASDs refer to the condition of subjects who have autistic behaviors secondary, however, to cerebral lesions and genetic or metabolic known diseases.

Mental retardation is frequently associated with autism in more than 75 % of cases (Gillberg and Coleman 1992), and some authors consider severe/profound mental retardation to be a clinical feature typical of non-idiopathic/syndromic ASDs patients. Others dispute this observation (Duca et al. 2011). Regardless, it is imperative to employ a diagnostic protocol to investigate the diseases that may be

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characterized by autistic behavior symptoms (Schaefer and Mendelshon 2008; Duca et al. 2011). A better understanding of the pathologies associated with ASDs may in fact provide additional genetic advice on the recurrence of medical disorders and may improve their prognoses and medical treatments.

According to Fombonne's 2009 report, ASDs prevalence is 60–70/10.000, with a male-to-female ratio of 3–4:1. In the past few years, ASDs prevalence has increased probably due to a better diagnosis sensibility and the impact of additional environmental factors on ASDs occurrence (Johnson et al. 2007).

Associated or Underlying Medical Conditions in Autism

Several medical diseases are reported in patients affected by autism. It is important to know and recognize associated medical conditions in ASDs for several reasons. First of all, other associated diseases may be treatable, and the resulting improvement can influence positively the patient's behavior, which may be generally impaired by other symptoms or painful conditions. For example, in ASDs the occurrence of epilepsy and EEG paroxysmal abnormalities is extremely frequent (Parmeggiani et al. 2010). Typical ASDs behavioral abnormalities such as staring, lack of responsiveness, or repetitive motor behavior may closely mimic epileptic seizures particularly in patients with language and communication skill impairments or with mental retardation. Moreover, epileptic seizures could cause additional problems in the development and learning capability of ASDs patients. An accurate recognition of the medical diseases associated with autism may also help to identify subgroups of ASDs with homogeneous phenotypic and genetic characteristics and foster a better understanding of the possible pathogenetic mechanisms responsible for ASDs. Epileptic seizures, sleep irregularities, metabolic disturbances, dental abnormalities, voiding problems, and feeding and gastrointestinal disorders are recognized as relevant associated or underlying medical problems in ASDs (Oliviè 2012). Parents, physicians, psychologists, and all operators involved in the care of these patients, not only during infancy but also during puberty and adulthood, should be aware that medical disorders could affect negatively the behavior and well-being of patients with autism. Moreover, all of these associated illnesses may be interrelated, for example, feeding disorders may depend upon gastrointestinal disturbances or sleep may be disrupted by gastrointestinal disorders, epileptic seizures, or depressive and anxiety symptoms.

Gastrointestinal Disorders in Autism

Since Kanner's first observations in 1943, also reporting on feeding problems in patients whom he described as affected by infantile autism, evidence has been produced that children with autism tend to have increased food selectivity and GI disorders. For this reason, the scientific community has grown increasingly interested in the role of the gut in autism.

Major Historical Perspectives

Two studies, dating to the 1970s, report, for the first time, GI problems in ASDs (Goodwin et al. 1971; Walker-Smith and Andrews 1972). In 1998, Wakefield and collaborators were the first to describe cases in which ileal-lymphoid-nodular hyperplasia and nonspecific colitis affected children with developmental disabilities. Their sample also included ASDs patients. Wakefield also argued for a possible relationship between autism and measles, mumps, and rubella (MMR) vaccine because endoscopic findings in children with autism revealed lymphoid nodular hyperplasia, mucosal abnormalities, and nonspecific inflammation in the intestine. Wakefield's highly contentious hypothesis, which was disputed by many, was that MMR vaccine enhanced the risk of autism in vulnerable children through GI mechanisms (Wakefield 1999); however, later epidemiologic data did not support this link. Nonetheless, the prospect of a connection between autistic behavior and GI disorders and the discovery of a possible, albeit controversial, gut nonspecific inflammation called for the attention of the scientific world. The behavior and cognitive impairments were considered to be due to what could be defined as an encephalopathy caused by increased intestinal permeability to exogenous peptides introduced with food intake, which led, in turn, to the disruption of the regulation of normal brain development.

Other studies have suggested a relationship between GI disorders and autism. For example, in 1999 Horvath and collaborators observed a number of GI disturbances, diagnosed with endoscopy, including reflux esophagitis, chronic gastritis and/or duodenitis, low level of carbohydrate digestive enzymes, and increased pancreato-biliary secretion after the administration of secretin in children with autism. In 2002, Torrente and collaborators compiled a comparative study of children with regressive autism, children with cerebral palsy and mental retardation, celiac disease patients, and control cases. The results showed that ASDs patients were affected by a focal or diffuse gastritis, a lymphocyte infiltration, and a dense subepithelial basement membrane IgG deposition. A link between autism and bowel inflammation of autoimmune origin or dysbiosis in particular clostridia antigens, which increase autoimmune processes, has also been reported. Recent theories, according to which inflammation, dysbiosis, and autoimmune mechanisms would be at the origin of bowel diseases, appear to support some studies describing the use of nonabsorbable antibiotics and antifungals in children with autism to relieve GI symptoms but also to help cognition and behavior. However, an improvement of autistic behavior has not been definitively proven.

In some cases, lactulose or macrogols were used to regulate bowel movements and counter chronic constipation resulting from a paralysis of the peristaltic movements caused by bacterial toxins. Finally, active peptides and other compounds including gluten and/or casein, present in diets that are not metabolized correctly, are believed to be responsible, along with food allergies, for behavior problems in autism. This has lead to an increased use of gluten- or casein-free diets as a form of medical intervention (Cubala-Kucharska 2010).

In recent years, several researchers have objected that no conclusive data are available on the condition that Wakefield termed as autistic enterocolitis and have insisted that more studies are needed to better define the connection between ASDs and the GI tract. In a subgroup of subjects affected simultaneously by ASDs and GI and immune system disorders, different mechanisms and multiple genes may be implicated in the etiopathogenesis. In 2008, Valicenti-McDermott and collaborators published a cross-sectional study with structured interviews of 100 children with ASDs. While the results of this study suggest that there is a correlation among language regression, familial history for autoimmune diseases, and GI symptoms, nevertheless, the authors conclude that further research is still needed to clarify the association among the autoimmune system, the GI tract, and phenotypic autistic traits. The recommendations for the evaluation and treatment of GI disorders in pediatric population are indeed useful also for ASDs patients, and they may help to improve the quality of life of these subjects (Buie et al. 2010).

Hypotheses About the Relationship Between the Gut and the Brain in ASDs

Several hypotheses have been formulated about the etiopathogenetic role that the interaction between the gut and the brain plays in causing autistic behaviors.

It has been found that compared to normal children affected by bowel inflammatory diseases, children with ASDs and GI disorders, who underwent biopsies of the duodenum, terminal ileum, and colon, present a more enhanced lymphocyte infiltration (helper and cytotoxic T cells, $CD19^+$ B cells). Additionally, Torrente and collaborators have reported that ASDs subjects show a pathologic deposition of IgG1 and IgG4 on the basolateral enterocyte and subepithelial basement membranes that is not seen, instead, in normal control children and in children with cerebral palsy and mental retardation (Torrente et al. 2002). A composition of gut microbial species has also been described to possibly compromise GI functions. For example, a lower level of Bifidobacterium and a colonization of Clostridium species may be responsible for the higher risk of developing food allergies and for the susceptibility to bowel inflammation in children. These observations all support the hypothesis that in a child with a genetic predisposition to ASDs, the immunologic and inflammatory factors described above may contribute to the manifestation of the phenotypic behavior or its severity (de Theije et al. 2011).

Intestinal permeability increases in patients with ASDs and also in their first-degree relatives (de Magistris et al. 2010). An augmented intestinal permeability, due to a chronic inflammation and induced by dietary antigens (exogenous peptides) and bacteria that interact with the immunological system, may create an immunological memory of the T and B cells, with secondary cell proliferation and cytokine release. Inflammations are also mediated by serotonin; interestingly, a high blood level and a low brain level of serotonin were found in patients with autism. Upon review of these data, it has been proposed that a high blood level of serotonin may be responsible for diarrhea and an altered motility of the intestine

and that the low level of serotonin in the brain may be the cause of behavioral and mood problems. The relationship between serotonin metabolism and autism still requires further investigation, particularly with regard to the use of such drugs as the selective serotonin reuptake inhibitors with ASDs patients. Food allergies may also cause an increased intestinal permeability. Food allergies are usually more frequent in children with autism than in healthy control children. Activated by an immunologic reaction, mast cells may cause the enteric neurons to transmit signals to the central nervous system through the vagal and spinal nerves (de Theije et al. 2011).

It has also been proposed that entering circulation from the intestine, the immune cells and their substances would pass the blood-brain barrier by diapedesis and active transport and reach the central nervous system. In this way, immunological reaction and intestinal inflammation would influence the brain and, as a result, the behavior of patients with autism. Lymphocyte migration across the blood-brain barrier highly increases upon immune activation; lymphocyte infiltration causes a rise in cytokines and chemokines which, in turn, may activate the microglia and influence neuronal functions. On the other hand, the microglia and astrocytes are important in regulating the immune responses in the central nervous system. Brain endothelial cells are themselves able to produce immune factors like prostaglandins, leukotrienes, cytokines, and chemokines; these may activate the microglia and astrocytes, which modulate neuronal functioning. A main component of Gram-negative bacteria, lipopolysaccharide, has also been considered as a causing factor of neuroinflammation since its plasma level appears to be related to enhanced intestinal permeability. Lipopolysaccharide, whose level increases in subjects with severe ASDs, may stimulate the endothelial brain cells to produce cytokines and render the blood-brain barrier more permeable, thus modulating neuroinflammation (de Theije et al. 2011).

Additional hypotheses consider maternal allergic diseases during pregnancy or the implication of other immune disorders or argue that the mammalian target of rapamycin (mTOR) – a kinase regulating cell growth and metabolism – is involved in protein synthesis-dependent synaptogenesis, suggesting that mTOR may also play a central role in directing immune response (de Theije et al. 2011).

Prevalence and Clinical Features of GI Disorders in ASDs

Subjects with ASDs frequently present GI symptoms. Although an association between GI disorders and autism has been suggested, the actual prevalence of GI disorders in autism is not completely known because epidemiologic and perspective studies are scanty (Erickson et al. 2005). The estimated prevalence of GI symptoms ranges from 9 % to 70 % and above (Buie et al. 2010); reported pathologies include gastroesophageal reflux disease, gastritis, esophagitis, inflammatory bowel disease, celiac disease, Crohn's disease, and colitis. The GI symptoms more frequently reported are constipation, diarrhea, bloating, belching, abdominal pain, reflux, vomiting, and flatulence. ASDs patients usually experience great difficulty at

verbally communicating a discomfort caused by GI diseases; for this reason, when they show disturbed or aggressive behaviors, hyperactivity, sleep disturbances, and feeding problems, these conditions may be interpreted erroneously, confounding the diagnosis. Independently of the etiopathogenetic role of permeability and gut inflammations described above, a simple discomfort unknown to the caregivers can be the cause of an ASDs patient's behavior regression.

The literature on the association between GI disturbances and autism includes clinical studies that compare, for example, subjects with autism with or without GI problems; subjects with autism and normal control subjects; ASDs, normal population, subjects with other neurological disabilities; and subjects affected by bowel diseases (Black et al. 2002; Molloy and Manning-Courtney 2003; Ibrahim et al. 2009; Nikolov et al. 2009; Whitehouse et al. 2011). Other studies draw attention to the prevalence and the clinical characteristics of GI disorders or consider gastrointestinal flora or histological and immunological data or both (Horvath et al. 1999; Horvath and Perman 2002; Valicenti-McDermott et al. 2008; Adams et al. 2011; Jyonouchi et al. 2011). The behavioral symptoms most frequently considered as indexes of the relationship between GI disorders and autism are language and developmental regression (Molloy and Manning-Courtney 2003; Valicenti-McDermott et al. 2008). In general, the conclusions offered by the studies on the association of GI disorders and autism are not consistent; for the most part, they show an occurrence of GI disorders in ASDs patients, but some of them neither show evidence of this relationship nor demonstrate that GI disorders actually affect developmental regression. In 2008, Barcia and collaborators reported, retrospectively, the occurrence of a celiac disease in 150 patients with ASDs, which was significantly higher ($p = 0.014$) in comparison with the general pediatric population. They also reported that after a period of gluten-free diet, while improvement in GI symptoms was observed, behavioral features remained the same as before (Barcia et al. 2008). Overall, there are no conclusive results, and to better define the relationship between GI disturbances and autism, further research is necessary that also considers prospective evaluations of wide samples, controlled dietary trials, and continued investigation into the function of the gut-brain axis (Erickson et al. 2005). Evidence-based guidelines for the diagnosis of GI disturbances in ASDs patients do not exist yet; only qualified suggestions made by a consensus group in 2010 are currently available (Buie et al. 2010).

Relationship Between Feeding and GI Disorders in ASDs

Feeding disorders are frequently described in children with disabilities and also in ASDs. They appear in children with ASDs generally around the sixth month of life (Emond et al. 2010). The prevalence ranges from 46 % to 89 %. Food selectivity is the predominant disorder; it affects about 70 % of the patients with ASDs and usually develops around the 15th month of life. Selectivity may be due to the texture, smell, odor, or color of foods. In patients with ASDs, energy intake and growth do not appear, in general, to be compromised. The causes of feeding

disorders are various – among the most common ones are GI disorders such as gastroesophageal reflux, food allergies, gastritis, colitis, and celiac disease; pharmacological treatments used for associated medical diseases; and primary behavioral problems as obsessive compulsive or repetitive behaviors, imitation impairment, and limited interests. In non-idiopathic ASDs patients, dysphagia may be caused by oral motor impairment. Feeding disorders may cause GI disorders, which, in turn, can be responsible for other clinical problems such as sleep disorders and impaired behavior in ASDs.

The etiopathogenesis of feeding disorders is complex. Researchers have surmised that sensory integration difficulties in ASDs and environmental and social factors like, for example, familial food selectivity or negative reinforcements of dietary habits may play a role in the development of feeding disorders (Schreck and Williams 2006). Parents themselves may perceive the dietary intake in children with ASDs as different from that in normal children. At present, there is no definitive conclusion regarding the causal relationship and interconnectedness between feeding problems and ASDs. In this instance too, additional studies are needed.

Diagnosis and Treatment of GI Disorders in Autism

It is very important to study the health conditions associated with ASDs. A sudden, unexplained, or atypical behavior as facial grimacing, constant eating or drinking, aggression, or self-injurious behaviors may correspond, especially in nonverbal subjects, to a discomfort connected with a GI disorder. In general, associated medical problems are treatable, and this helps ASDs patients and their families to feel better. Equally important are the reconstruction of the medical history of a patient, a comprehensive review of familial and personal data, physical examination, consideration of weight for age and height for age, body mass index and growth variation, and the performance of several tests such as the analysis of stool specimens for enteric pathogens or parasites, allergy tests, electrolytes/osmolarity, pancreas and liver function tests, search of Helicobacter pylori and celiac disease, immunoglobulins, assessment of nutritional status, and abdominal roentgenogram for gas and abdominal retention of stool. Endoscopy and colonoscopy are also performed, frequently using sedation because ASDs patients are not cooperative. Genetic tests are helpful in non-idiopathic ASDs cases because only few data have been reported on the association with GI disorders in these subjects (Buie et al. 2010; Duca et al. 2011). A consensus report, which, in 2010, reviewed the literature on the evaluation and treatment of GI problems in children with ASDs, concluded that evidence-based recommendations on the topic are not yet available and advised that patients with ASDs, who frequently have symptoms that may be atypical, receive the same diagnostic workup and guidelines for GI symptoms as pediatric patients without autism (Buie et al. 2010). Pediatricians, allergists, gastroenterologists, child neurologists and psychiatrists, psychologists, dietitians, and nutritionists should all be involved in the supervision and treatment of ASDs patients with GI disorders.

The treatment of GI disorders generally depends on the underlying dysfunctions that are diagnosed, for example, a celiac disease may be treated with a gluten-free diet. As the GI symptoms improve, so do the disrupted behavior of the suffering patient and the quality of his or her life. In ASDs medical therapy is often utilized to improve behavioral symptoms; in these cases, treatments are usually selected on the basis of the supposed etiopathogenesis of the autistic behavior. Some therapies are suggested based on the gut-brain axis model. At present, antibiotic or antifungal therapies are not recommended for ASDs patients without a clear intestinal bacterial or fungal disease. Although they are frequently used with ASDs patients (Hanson et al. 2007), medical interventions employing probiotics, vitamins/minerals, omega-3 fatty acids, casein- and/or gluten-free diets, as well as other products typical of the complementary and alternative medicine require further investigation to assess their actual effectiveness. It must be underscored that using a restricted diet as a form of intervention requires continuous professional supervision to identify and eventually treat nutritional inadequacies. Given the current status of our knowledge on the subject, it is advisable to apply only those medical treatments that are rooted in evidence-based practice and have a solid scientific foundation. The integration of behavioral educational and medical cares may be most beneficial to ASDs patients.

Conclusions

GI disorders frequently affect autistic patients and may be the cause of their behavioral impairment. Autistic patients are often unable to communicate their discomfort, and for this reason, their conditions may not receive a proper diagnosis. Since the 1970s, several hypotheses have been formulated and reported in literature about the possibility of a correlation between GI disorders and autism. Although the data regarding the gut-brain axis model, showing an intriguing interaction of the immunological system with the central nervous system, are encouraging, at present the research on the subject is limited to case reports and observational or uncontrolled studies. Further investigation is necessary to clarify the etiopathogenesis and management of GI disorders in autism. However, it is evident that ASDs patients need the same recommendations on diagnostic interventions and management of GI problems as children without autism. ASDs children can benefit from the evaluation and treatments of GI disorders.

Key Terms

Autism spectrum disorders. Autism spectrum disorders are a group of behavioral pathologies characterized by impairment of social interaction and of verbal and nonverbal communication, poor social skills, restricted repertoire of interests, and repetitive behaviors. This term is used in the forthcoming fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

Behavior regression. Loss of previously acquired competences regarding one's behavior, often accompanied by a loss of verbal and nonverbal communication abilities. These problems may be typical of the autism phenotype.

Feeding disorders. A group of feeding problems, age-specific and particularly relevant in children with disabilities. Examples include food refusal, food selectivity, picky eating patterns, and particular food preferences. If they become chronic, they may be associated with growth retardation, malnutrition, developmental and psychological deficits, and social difficulties.

Gastrointestinal disorders. Diseases affecting the esophagus, the stomach, and the intestine, such as gastroesophageal reflux disease, esophagitis, gastritis, inflammatory bowel disease, celiac disease, Crohn's disease, and colitis.

Gastrointestinal symptoms. Clinical symptoms characterizing gastrointestinal disorders. They typically include constipation, diarrhea, bloating, belching, abdominal pain, reflux, vomiting, and flatulence.

Key Facts of DSM-IV

- The DSM is the Statistical Manual of Mental Disorders published by the American Psychiatric Association; it provides criteria for the diagnosis of a broad range of mental disorders.
- The first edition appeared in 1952.
- DSM-IV is the manual's fourth edition and was published in 1994; DSM-IV TR, published in 2000, provides a text revision of the fourth edition.
- The DSM-IV identifies five main diagnostic categories (or axes) for mental disorders, addressing clinical disorders (Axis I), personality disorders and intellectual disabilities (Axis II), physical disorders (Axis III), and psychosocial and environmental factors affecting mental disorders (Axis IV) and providing the Children's Global Assessment Scale (Axis V).
- The manual's fifth edition (DSM-5) is forthcoming in 2013.

Key Facts of the Gut-Brain Axis

- The gut-brain axis identifies and correlates possible pathways for immunologic factors of gastrointestinal origin, which would be able to modulate neuronal functions and ultimately behavior in autism.
- Several levels are described in these pathways.
- Variables considered include gut inflammation, increased intestinal permeability, and immunological reaction; serotonin level, food allergies, and maternal allergies during pregnancy may also be important factors in this model.
- The blood-brain barrier affects the relationship between the immune system and neural modulation.

- mTOR may represent a possible link between the immune and the central nervous systems in causing behavior disorders in ASDs.
- All the hypotheses based on the gut-brain axis need further investigation in order to develop new possible treatments of behavioral symptoms in ASDs.

Key Facts of Celiac Disease

- Celiac disease is an immune-mediated, chronic, multisystemic disorder triggered by gluten ingestion in genetically predisposed subjects in any age of life.
- Prevalence of celiac disease in Europe and in North America ranges from 1:150 to 1:250.
- The disease is responsible for several symptoms in different organs of the body.
- Major symptoms of the typical celiac disease are intestinal.
- Latent and atypical forms of the disease also exist, the latter being characterized by feeding problems, growth failure, anemia, or dermatologic signs.
- Such neurologic or psychiatric symptoms as epilepsy, headache, and autism are also reported.

Key Facts of Behavior Treatments in Autism

- Behavior treatments aim at improving autistic behavior by fostering social reciprocity and daily life autonomy, by facilitating verbal and nonverbal communication, and by attempting at overcoming restricted interests and behaviors.
- In order to be effective, implementation of these educational programs has to occur early in life.
- It is necessary that treatments be sustained over time.
- Approaches to the treatment of autistic behaviors include applied behavior analysis (ABA), developmental models, structured teaching, speech and language therapy, social skill therapy, and occupational therapy.
- Intensive ABA treatment has improved children's global and intellectual functioning.

Key Fact of Complementary and Alternative Medicine

- The term complementary and alternative medicine refers to practices, products, or medical health-care systems that are considered outside the realm of evidence-based medicine.
- It covers various areas such as the mind-body medicine, the biologically based practice, the manipulative and body-based practice, and the energy medicine.

- Complementary and alternative medicine interventions such as gluten- and casein-free diets and the administration of vitamins and minerals are frequently used in autism.
- Alternative therapies and interventions lack predictive validity.
- Further controlled and prospective studies and possibly dietary trials are necessary to promote evidence-based guidelines.

Summary Points

- This chapter focuses on gastrointestinal (GI) disorders and symptoms in autism.
- The estimated prevalence of GI symptoms in autism ranges from 9 % to 70 % or higher.
- Patients with autism are very often unable to verbally communicate a discomfort caused by a GI disease; disturbed or aggressive behaviors, hyperactivity, sleep disturbances, and feeding problems may appear as a consequence.
- Intriguing hypotheses have been formulated about a gut-brain axis model describing communication pathways between the immune and central nervous systems.
- Further research is needed to clarify the relationship between GI disorders and autism.
- Children with autism require the same recommendations on diagnostic interventions and management of GI problems as children without autism.

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