Neurogenic bowel dysfunction in patients with spinal cord injury, myelomeningocele, multiple sclerosis and Parkinson’s disease

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Abstract

Exciting new features have been described concerning neurogenic bowel dysfunction, including interactions between the central nervous system, the enteric nervous system, axonal injury, neuronal loss, neurotransmission of noxious and non-noxious stimuli, and the fields of gastroenterology and neurology. Patients with spinal cord injury, myelomeningocele, multiple sclerosis and Parkinson’s disease present with serious upper and lower bowel dysfunctions characterized by constipation, incontinence, gastrointestinal motor dysfunction and altered visceral sensitivity. Spinal cord injury is associated with severe autonomic dysfunction, and bowel dysfunction is a major physical and psychological burden for these patients. An adult myelomeningocele patient commonly has multiple problems reflecting the multisystemic nature of the disease. Multiple sclerosis is a neurodegenerative disorder in which axonal injury, neuronal loss, and atrophy of the central nervous system can lead to permanent neurological damage and clinical disability. Parkinson’s disease is a multisystem disorder involving dopaminergic, noradrenergic, serotonergic and cholinergic systems, characterized by motor and non-motor symptoms. Parkinson’s disease affects several neuronal structures outside the substantia nigra, among which is the enteric nervous system. Recent reports have shown that the lesions in the enteric nervous system occur in very early stages of the disease, even before the involvement of the central nervous system. This has led to the postulation that the enteric nervous system could be critical in the pathophysiology of Parkinson’s disease, as it could represent the point of entry for a putative environmental factor to initiate the pathological process. This review covers the data related to the etiology, epidemiology, clinical expression, pathophysiology, genetic aspects, gastrointestinal motor dysfunction, visceral sensitivity, management, prevention and prognosis of neurogenic bowel dysfunction patients with these neurological diseases. Embryological, morphological and experimental studies on animal models and humans are also taken into account.

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Key words: Neurogenic bowel dysfunction; Spinal cord injury; Myelomeningocele; Multiple sclerosis; Parkinson’s disease; Central nervous system; Enteric nervous system

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INTRODUCTION
Exciting new features have been described concerning neurogenic bowel dysfunctions (NBD), including interactions between the central nervous system (CNS), enteric nervous system (ENS), neurotransmission of noxious and non-noxious stimuli, and the fields of gastroenterology and neurology. Patients with spinal cord injury (SCI), myelomeningocele (MMC), multiple sclerosis (MS) and Parkinson’s disease (PD) present with autonomic dysreflexia, serious upper and lower NBD characterized by constipation, incontinence, severe gastrointestinal (GI) motor dysfunction and altered visceral sensitivity. SCI is associated with severe autonomic dysfunction, with bowel dysfunction as a major physical and psychological burden for these patients. The outcome of MMC patients is fraught with multiple problems reflecting the multisystemic nature of the disease. MS is a devastating autoimmune disease with symptoms dependent on the clinical type and the site of lesions. It has been considered a chronic, inflammatory disorder of the central white matter in which demyelination results in the ensuing physical disability. Recently, MS is viewed as a neurodegenerative disorder in which axonal injury, neuronal loss, and atrophy of the CNS can lead to permanent neurological and clinical disability, in which mitochondrial DNA defects are involved. PD is considered as a disorder involving dopaminergic, noradrenergic, serotonergic, and cholinergic systems, characterized by motor and non-motor symptoms. Interestingly, in recent years it has become evident that PD affects several neuronal structures outside the substantia nigra, between which are the ENS. Recent reports have shown that the lesions in the ENS occur at a very early stage of the disease, even before the involvement of the CNS. This has led to the hypothesis that the ENS could be critical in the pathophysiology of PD, as it could represent a point of entry for a putative environmental factor to initiate the pathological process. This review covers the data related to etiology, epidemiology, clinical aspects, pathophysiology, genetics, gastrointestinal motor dysfunction, visceral sensitivity, management, prevention, and prognosis of NBD patients with these neurological diseases. Embryologic, morphological and experimental studies on animal models and humans are also taken into account.

LITERATURE REVIEW
Search strategy
A Medline search was performed using the following subject headings: spinal cord injury, neural tube defects (NTD), myelomeningocele, multiple sclerosis, Parkinson’s disease, animal models, and human. The date of the most recent search was February 28, 2011.

Selection criteria
Clinical, epidemiological, pathophysiological, motor dys-

function, visceral sensitivity and experimental studies on animal models and patients with SCI, MMC, MS, PD, as well as specific therapies for these neurological diseases involving bowel dysfunction were reviewed. Issues related to genetics, embryology, morphology, prevention and prognosis were also taken into account.

Data collection and analysis
A total of 177 articles were included in the analysis.

ETIOLOGY
SCI etiology is generally divided into traumatic and non-traumatic causes. The onset of NTD occurs at 21-28 d of embryonic development. MMC results from lack of closure of the neural tube during this stage. Its etiology is complex, involving both genetic and environmental factors. A maternal effect as well as a gender-influenced effect, have been suggested as part of its etiology. Although there are more than 200 small animal models with NTD, most of them do not replicate the human disease phenotype. The candidate genes studied for risk association with spina bifida include those important in folic acid metabolism, glucose metabolism, retinoid metabolism, apoptosis, and those that regulate transcription in early embryogenesis.

MS is an etiologically unknown disease with no cure. It is the leading cause of neurological disability in young adults, affecting over two million people worldwide. MS has been considered a chronic, inflammatory disorder of the CNS white matter in which demyelination results in the ensuing physical disability. Recently, MS has become increasingly viewed as a neurodegenerative disorder in which axonal injury, neuronal loss, and atrophy of the CNS can lead to permanent neurological damage and clinical disability.

GI dysmotility in PD has been attributed to the peripheral neurotropic action. Recently, it has been suggested that sporadic PD has a long prodromal period and several nonmotor features develop during this period. Hawkes et al proposed that a neurotropic viral pathogen may enter the brain via nasal route with anterograde progression into the temporal lobe or via gastric route, secondary to the swallowing of nasal secretions. These might contain the neurotropic pathogen that, after penetration of the epithelial lining, could enter the axons of the Meissner plexus and, through transsynaptic transmission, reach the preganglionic parasympathetic motor neurons of the vagus nerve. This would allow retrograde transport into the medulla and from there into the pons and midbrain until the substantia nigra is reached. A summary of suggested pathogenesis of GI disorders underlying PD is shown in Table 1.

EPIDEMIOLOGY
Traumatic SCI represents a significant public health problem
Table 1  Suggested pathogenesis of gastrointestinal disorders underlying Parkinson’s disease

| GI pathogenesis                                      | Disorder                                      |
|------------------------------------------------------|-----------------------------------------------|
| Peripheral neurotoxine action                        | Intestinal cells of Cajal involvement [18]   |
| GI flora? Neurotropic viral pathogen                 | GI disorders [46]                            |
| GI flora? Helicobacter pylori                        | Modified I-dopa pharmacokinetics [42]        |
| GI dysmotility: Early lesions in the enteric nervous system | GI dysfunctions [13,10]                      |
| GI dysmotility: Disruption in parts of the CNS       | Neurogenic dysphasgia [26]                   |
| GI dysmotility: Lewy bodies in esophageal myenteric plexuses | Manometric abnormalities [10,26]             |
| GI dysmotility: Reduction amplitude of peristaltic contractions | Decreased gastric motility [31]             |
| GI dysmotility: Gastric pacemaker disturbances       | Gastric dyssyrhythmia [16]                   |
| GI dysmotility: Loss of enteric dopaminergic neurons | Changes in colon motility [21]               |
| Neurotransmitter dysfunction: Altered enteric nitric systems | Disturbed distal gut transit [29]           |
| Neurohormone involvement: Neureotensin               | GI disorders [40]                            |
| Levodopa                                             | Altered oral phase of deglutition [29]       |
| Monoamine dysfunction                                | Nonmotor symptoms [15]                       |

GI: Gastrointestinal; CNS: Central nervous system.

worldwide [31]. Each year, 11,000 individuals are estimated to have SCI in the United States [23] with a mortality rate of 27.4 per million people. An annual incidence of 33.6 per million is reported in Greece and 19.5 per million in Sweden [22], while in Denmark the number of SCI patients is about 3000.

NTD is the second most common birth defect, with an incidence of 1/1000. MMC is the most common subtype (66.9%) [14]. NTD is rarely reported in black Americans and Japanese, but is not so rare in Cameroonian and sub-Saharan black Africans, with an incidence of 1.9 cases per 1000 births [25]. In Switzerland, the incidence of NTD in children is 0.13 per thousand, corresponding to 9-10 affected newborns each year [18], while in Thailand, the incidence is 0.67 per 1000 births [24]. NTD is reported in adolescents aged 15-18 years [26] and in young adults aged 20-23 years [8].

MS affects young and middle-aged people [27], the mean age at disease onset is 30.7 ± 6.4 years, and it is believed that pregnancy, postpartum status and vaccines [9], as well as infection with Epstein-Barr virus [30], may influence the onset and course of the disease. An increase in females and an almost universal increase in the prevalence and incidence have been reported, challenging the theory of a geographical gradient of incidence in Europe and North America [30]. It affects 100 000 people in the United Kingdom [30], with a prevalence of 30.9/100 000 in Herzegovina [31]. An association between the risk of MS and the season of birth suggested that decreased exposure to the sunshine in the winter leading to low vitamin D levels during pregnancy is an area that needs further research [32].

PD is the second most common neurodegenerative disease after Alzheimer’s disease [11], affecting one million people in the United States each year [13], and 20% of the population aged > 65 years in Mexico [34]. It is described in sporadic and familial forms [30] (at least 2 individuals are affected within 2-3 consecutive generations of a family).

**DIAGNOSIS, CLINICAL DATA AND SYMPTOMS**

Neurophsyologic testing of the sacral reflex is useful in the diagnosis of sacral lower motor neuron lesions, and increased elicitation of the penilo-cavernous reflex is reported in patients with chronic SCI [31]. Patients with SCI may present [4] with brain anatomical changes of loss of motor control, chronic neuropathic pain [37] and abdominal pain [38], urinary and sexual dysfunction [39], decubitus [40], neurogenic immune depression syndrome [42], and an increased risk of having a depressive disorder [43]. Spinal cord lesions affect colorectal motility, anorectal sensation, anal sphincter function, and cause neurogenic constipation [44]. Defecation is abnormal in 68% of cases, digital stimulation is required by 20%, suppositories by 10% and enemas by 28% of cases. Time spent in each defecation is more than 30 min in 24% cases. In children aged four years or older, daily fecal incontinence occurred in 14% and weekly incontinence in 14% cases [45]. SCI patients usually do not perceive the normal desire for defecation, rather describing it as abdominal distension, hardened or cool abdomen, hardening of the legs, abdominal pain, chills and dizziness, itching of the head, and a feeling of pain at the sacrum level [1]. Additionally, SCI subjects may develop autonomic dysreflexia in response to noxious stimuli [46]. Cardiovascular dysregulation, characterized by paroxysmal high blood pressure episodes, is the most prominent feature and is precipitated by manual emptying of rectal contents and by gastric and bowel distension [27]. Regarding the gravity of this issue, an NBD score (0-6 very minor, 7-9 minor, 10-13 moderate and 14 severe) [48], an international bowel function basic [49] and extended [50] SCI data set, as well as an international standard to document the remaining autonomic function after SCI [40] have been developed.

Prenatal screening with α-fetoprotein and ultrasonography have allowed the prenatal diagnosis of NTD in current obstetric care [41]. In an animal model with naturally occurring spina bifida (curly tail/loop tail mouse), using standard enzyme linked immunosorbent assay techniques, detection of amniotic fluid levels of the neurofilament heavy chain, glial acidic fibrillary protein and S100B, seems to provide important information for balancing the risks and benefits, both to mother and child, of in utero...
surgery for MMC[58]. Colorectal problems are common in children with MMC and their impact on the quality of life becomes more severe as the child grows up.

Diagnosis of MS is made according to the McDonald and the Poser criteria, with the McDonald criteria showing a higher sensitivity for diagnosis[53]. Bowel symptoms are reported to be common in MS, including constipation (29%-43%) and fecal incontinence (over 50%), and 34% of patients spending more than 30 min a day managing their bowel movement[30]. Neurogenic dysphagia is also present[84]. Autonomic dysreflexia may occur in MS[55], characterized by hypertensive attacks, palpitations, difficulty in breathing, headaches and flushing[86]. Autonomic symptoms are disorders of micturition, impotence, sudomotor and GI disturbances, orthostatic intolerance as well as sleep disorders[57]. Neuropsychiatric symptoms include abnormalities in cognition, mood and behavior (major depression, fatigue, bipolar disorder, euphoria, pathological laughing and crying, anxiety, psychosis and personality changes). Major depression is a common neuropsychiatric disorder, with an approximate 50% lifetime prevalence rate[58]. Pediatric MS has been identified as an important childhood acquired neurologic disease[59].

GI diagnosis in PD[60] includes history, clinical examination, barium meal, breast disorders, stomach scintigraphy and colonic transit time[61]. Oropharyngeal dysphagia is recognized by difficulty in transferring a food bolus from the mouth to the esophagus or by signs and symptoms of aspiration pneumonia or nasal regurgitation[81]. PD is actually considered a neurodegenerative process that affects several neuronal structures outside the substantia nigra. Reports have shown that the lesions in the ENS occurred at a very early stage of the disease, even before CNS involvement[10]. GI symptoms are very important, as GI diseases may also display neurological dysfunction as part of their clinical picture[81]. PD patients have motor and non-motor fluctuations classified into three groups: autonomic, psychiatric, and sensory[84]. GI dysfunction is the most common non-motor symptom which comprises sialorrhea, swallowing disorders[85], dysphagia[86], acid regurgitation, pyrosis[87], early satiety, weight loss, constipation[86], incomplete rectal emptying, the need for assisted defecation and an increased need for oral laxatives[80].

The association between a polymorphism in the ABCB1 gene and PD has been observed. The ATP-binding cassette, sub-family B, member 1 (ABCB1) gene encoding P-glycoprotein (P-gp), has been implicated in the pathophysiology of PD due to its role in regulating the transport of endogenous molecules and exogenous toxins. ABCB1 polymorphisms thus constitute an example of how genetic predisposition and environmental influences may combine to increase the risk of PD[71]. On the other hand, extensive ENS abnormalities in mice transgenic for PD-associated α-synuclein gene mutations precede CNS changes. Most PD is sporadic and of unknown etiology, but a fraction is familial. Among familial forms of PD, a small portion is caused by missense (A53T, A30P and E46K) and copy number mutations in SNCA, which encodes α-synuclein, a primary protein constituent of Lewy bodies, the pathognomonic protein aggregates found in neurons in PD[72].

### Gastrointestinal motor dysfunction and visceral sensitivity

Fecal incontinence in SCI, MMC and MS is mainly due to abnormal rectosigmoid compliance and recto-anal reflexes, loss of recto-anal sensitivity and loss of voluntary control of the external and sphincter[73]. On the other hand, constipation is probably due to immobilization, abnormal colonic contractility, tone and recto-anal reflexes, or side effects from medication. SCI patients have a higher incidence of esophagitis and esophageal motor abnormalities[74], gastric stasis, paralytic ileus, abdominal distension[75], partial or complete loss of the sensations upon defecation, constipation[76], hemorrhoids[76], and need for assisted digital evacuation than controls[77]. Studies have shown a range of neurological alterations, such as low amplitude, slowly propagating abnormal peristaltic esophageal contraction[78], a decrease in phase III of the interdigestive motor complex[79], reduction in gastric emptying[79], delayed GI transit, higher colonic myoelectric activity, reduced emptying of the left colon, and a suboptimal postprandial colonic response[79]. Visceral sensitivity testing according to Wietek et al[80] may be a future requirement, in addition to the American Spinal Injury Association (ASIA) criteria, in the assessment of the completeness of cord lesions in patients diagnosed with complete spinal cord transaction, as some report the sensation of distension of the rectum. In our laboratory, with barostat methodology, we found that complete supracaudal SCI patients preserve rectal sensation, and present with impaired rectal tone and impaired response to food. This data supports the fact that barostat sensitivity studies can complement ASIA criteria to confirm a complete injury. Our results also suggest that intact neural transmission between the spinal cord and higher centers is essential for noxious stimulus, but not for non-noxious stimuli, that patients with supracaudal lesions may present PP visceral hypersensitivity, and that incontinence and constipation may not be related solely to continuity of the spinal cord[81]. Sutoor et al[82], using
Table 2 Suggested pathogenesis of gastrointestinal disorders underlying spinal cord injury, myelomeningocele and multiple sclerosis

| Disease                      | GI pathogenesis                      | Disorder                        |
|------------------------------|--------------------------------------|---------------------------------|
| Spinal cord injury           | Abnormal rectosigmoid compliance     | Fecal incontinence               |
| Myelomeningocele             | Loss of recto-anal sensitivity       | Autonomic dysreflexia            |
| Multiple sclerosis           | Loss of voluntary control of the external anal sphincter | Constipation                    |
| Spinal cord injury           | Immobilization, abnormal colonic contractility, side effects of constipation | Myelomeningocele medication     |
| Myelomeningocele             | Paradoxical puborectalis contraction | Ventriculoperitoneal shunt malfunction |
| Myelomeningocele             | Bladder distension                   | Constipation and impaired rectal tone and response to food |
| Myelomeningocele             | Severe constipation                  | Cardiovascular dysregulation     |
| Myelomeningocele             | Higher spinal level of cord lesion, completeness of cord injury and longer duration of injury | Autonomic dysreflexia            |
| Spinal cord injury           | Noxious stimulus                     | Severe neurogenic bowel dysfunction |
| Spinal cord injury           | Manual emptying of rectal contents and gastric and bowel distension |                 |

a dual barostat in six cervical SCI patients without NBD, reported that intact neural transmission between the spinal cord and higher centers is not essential for normal colorectal motor response from feeding to distension. Lumbosacral neuropathy was demonstrated in 90% of SCI subjects using translumbar and trans-sacral motor-evoked potentials.

In MMC, studies have revealed swallowing disorders characterized by difficulty in bolus formation, nasopharyngeal and gastroesophageal reflux, tracheobronchial aspiration, and vocal cord paralysis, as well as a longer mean colonic transit time not related to the level of the spinal lesion and reduction in anal sphincter pressure. Ventriculoperitoneal shunt malfunction may occur in patients with MMC, and severe constipation that increases intra-abdominal pressure resulting in raised intracranial pressure, seems to be one of the causes. Visceral sensitivity studies with the barostat reveal that constipated children with MMC present with impaired rectal tone, impaired response to food and postprandial visceral hypersensitivity.

GI dysfunction occurs in MS as in other neurologic diseases. Slow gastric emptying rate, increased colonic transit time, absent PP colonic motor and myoelectric responses, altered maximal contraction pressures and anal inhibitory reflex threshold, impaired function of the external anal sphincter, and increased thresholds of conscious rectal sensation have been reported. Paradoxical puborectalis contraction is common in MS patients with constipation and it seems that autonomic dysreflexia occurs due to bladder distension. A summary of suggested pathogenesis of GI disorders underlying spinal cord injury, myelomeningocele, and multiple sclerosis is shown in Table 2.

In PD, dysphagia, impaired gastric emptying and constipation may precede its clinical diagnosis for years. ENS involvement could be critical as it may represent a point of entry for a putative environmental factor to initiate the pathological process. On the other hand, the mechanisms related to enteric autonomic dysfunctions may involve the enteric dopaminergic or nitricergic systems. It has been reported that rats with a unilateral 6-hydroxydopamine lesion of nigrostriatal dopaminergic neurons develop marked inhibition of propulsive activity compared with sham-operated controls. Results suggest that disturbed distal intestinal transit may occur as a consequence of reduced propulsive motility, probably due to an impairment of a nitric oxide-mediated descending inhibition during peristalsis. Neurogenic dysphagia may also appear in PD. It may be caused by a disruption in different parts of the CNS (supranuclear level, level of motor and sensory nuclei taking part in the swallowing process and peripheral nerve level) or a neuromuscular disorder. It is also suggested that levodopa plays a role in the oral phase of deglutition in PD. Constipation is present in up to 50% of PD cases and seems to be correlated with manometric irregularities. Castell et al. have described esophageal manometric abnormalities in 73% of PD patients characterized by complete aperistalsis or multiple simultaneous contractions (diffuse esophageal spasm) of the distal esophagus. They also reported repetitive proximal esophageal contractions, a very interesting finding supporting a previous report of a link between PD, achalasia, and scleroderma (e.g., PD and achalasia have Lewy bodies in the esophageal myenteric plexuses and the substantia nigra, as well as evidence of degeneration of the dorsal motor nucleus of the vagus), and esophageal manometric abnormalities were found in these three diseases. A link between PD and Helicobacter pylori has also been described, where HP eradication may improve the clinical status of infected patients with PD and motor fluctuations by modifying l-dopa pharmacokinetics. Neurotensin, a 13 amino acid neurohormone located in the synaptic vesicles and released from the neuronal terminals in a calcium-dependent manner, is involved in the pathophysiology of PD and other neurodegenerative conditions. Constipation and gastric atony are important
non-motor symptoms\textsuperscript{104}. There is a trend toward a decreased gastric motility in PD patients as compared with healthy controls due mainly to a significant reduction in the amplitude of peristaltic contractions\textsuperscript{105}; other authors have found gastric dysrhythmias indicating gastric pacemaker disturbances\textsuperscript{106}. Slow transit in the colon has been reported\textsuperscript{107}, and using ano-rectal manometry, decreased basal anal sphincter pressures, prominent phasic fluctuations on squeeze pressure, and a hyper-contractile external sphincter response to the rectosphincteric reflex have been documented. It has also been suggested that dystonia of the external anal sphincter causes difficult rectal evacuation and the loss of dopaminergic neurons in the ENS may lead to slow-transit constipation\textsuperscript{70}.

**MANAGEMENT**

Managing SCI bowel function is complex, time consuming and remains conservative\textsuperscript{73}. The use of manual evacuation\textsuperscript{108}, treatment with oral laxatives\textsuperscript{109} and abdominal massage\textsuperscript{109} have all been reported. Transanal irrigation is reported safe and can be used in many patients suffering from NBD\textsuperscript{111}, its results represent a lower total cost than conservative bowel management\textsuperscript{112}; however, its rate of success is only 35% after 3 years\textsuperscript{110}. Recent approaches include sacral neuromodulation\textsuperscript{112} and dorsal penile/clitoral nerve neuromodulation for the treatment of constipation, as well as magnetic stimulation for NBD treatment\textsuperscript{113}. Other options include colostomy, ileostomy, Malone anterograde continence enema, and sacral anterior root stimulator implantation\textsuperscript{114}. However, good quality research data is needed to evaluate the effects of these treatments for this condition.

For MMC patients with constipation, polyethylene glycol\textsuperscript{115,116} and the use of transanal irrigation\textsuperscript{116} seem to be effective, however, a majority of children found the procedure time consuming and did not help them to achieve independence at the toilet\textsuperscript{117}. For constipation, the approaches included intravesical\textsuperscript{118} and transrectal electro-stimulation\textsuperscript{119}; nevertheless these procedures lack well-designed controlled trials. For constipation and incontinence, biofeedback is used\textsuperscript{120}. Surgical closure of MMC is usually performed in the early postnatal period, however, not all patients benefit from fetal surgery in the same way\textsuperscript{121}. The management of cervical MMC is early surgical treatment with microneurosurgical techniques. Surgical excision of the lesions with intradural exploration of the sac to release any potential adhesion bands is safe and effective\textsuperscript{122}. The current therapies for MS are few, symptom-related, and experimental\textsuperscript{8}. In patients seen due to constipation, incontinence, or a combination of these symptoms a beneficial effect of biofeedback was attributed to some but not to all patients\textsuperscript{123}. Other approaches include oral administration of probiotic bacteria, *Lactobacillus casei* and *Bifidobacterium breve*, which do not seem to exacerbate neurological symptoms\textsuperscript{124}. An overactive bladder is successfully treated in 51% of cases with anticholinergic medication\textsuperscript{125}. The use of agonists or antagonists of prostaglandin-receptors may be considered as a new therapeutic protocol in MS. The reason is that prostaglandins as arachidonic acid-derived autacoids play a role in the modulation of many physiological systems including the CNS, and its production is associated with inflammation, which is a feature in MS\textsuperscript{126}.

Levodopa, a prodrug of dopamine, is one of the main treatment options in PD\textsuperscript{127}. However, in contrast to motor disorders, pelvic autonomic dysfunction is often refractory to levodopa treatment\textsuperscript{128}. One point to bear in mind is that treatments should facilitate intestinal absorption of levodopa\textsuperscript{126}. Current levodopa products are formulated with aromatic amino acid decarboxylase inhibitors such as carbidopa or benserazide to prevent the metabolism of levodopa in the GI tract and systemic circulation\textsuperscript{127}. Food appears to affect the absorption of levodopa, but its effects vary with formulations and studies suggest that a high protein diet may compete with the uptake of levodopa into the brain, thus resulting in reduced levodopa effects\textsuperscript{127}. Regarding disturbed motility of the upper GI-tract, hypersalivation is reported to be reduced by anticholinergics or botulinum toxin injections\textsuperscript{40}, while therapy for dysphagia includes rehabilitative, surgical, and pharmacologic treatments\textsuperscript{129}. Regarding constipation, tegaserod improves both bowel movement frequency and stool consistency\textsuperscript{130}. Mosapride citrate, a 5-HT4 agonist and partial 5-HT3 antagonist, in contrast to cisapride, does not block K (\(+\)) channels or D2 dopaminergic receptors\textsuperscript{131}. Other prokinetics include metoclopramide, domperidone, trimetrex, cis-apride, prucalopride, and itopride\textsuperscript{132}. Polyethylene glycol\textsuperscript{133}, functional magnetic stimulation\textsuperscript{134}, and psyllium are also used\textsuperscript{134}. However, the clinical significance of any of these results is difficult to interpret and it is not possible to draw any recommendation for bowel care from published trials, until well-designed controlled trials with adequate numbers of patients and clinically relevant outcome measures become available\textsuperscript{134}. Recently, stem cells have been used as an alternate source of biological material for neural transplantation to treat PD. The potential benefits for this are relief of parkinsonian symptoms and a reduction in the doses of parkinsonian drugs employed. However, the potential risks include tumor formation, inappropriate stem cell migration, immune rejection of transplanted stem cells, hemorrhage during neurosurgery and postoperative infection\textsuperscript{135}.

**PREVENTION AND PREDICTORS**

An analysis of predictors of severe NBD in SCI shows that those with a cervical injury or a thoracic injury had a higher risk of severe NBD than those with a lumbar spine injury. Also those classified as ASIA A had a 12.8-fold higher risk of severe NBD than persons with ASIA D. Besides, a longer duration of injury (\(\geq 10\) years) was considered as another risk factor of severe NBD. Moderate-to-severe depression was associated with reduced...
bowel function. The results showed that a higher spinal level of cord lesion, completeness of cord injury and a longer duration of injury (≥ 10 years) could predict the severity of NBD in patients with SCI\[20\]. It is reported that clinical variables are not the best predictors of long-term mortality in SCI. Instead, the significant effect of poor social participation and functional limitations seem to persist after adjustment for other variables\[136\].

Folic acid supplementation reduced the incidence of NTD in several geographical regions. However, the incidence is still high and associated with a serious morbidity\[137\]. A study done in newborn babies with NTD and their mothers revealed an association between NTD and decreased hair zinc levels, so large population-based studies are recommended to confirm the association between zinc and NTD\[138\]. The prevalence of scoliosis in patients with MMC has been reported to be as high as 80%-90%. A study aiming to determine clinical and radiographic predictors of scoliosis in patients with MMC reported that the clinical motor level, ambulatory status, and the level of the last intact laminar arch are predictive factors for the development of scoliosis. It is suggested that in patients with MMC, the term scoliosis should be reserved for curves of ≥ 20 degrees, it is also noteworthy that new curves may continue to develop until the age of fifteen years\[139\]. Other authors attempting to obtain a spine deformity predictor based on a neurological classification performed at five years of age report that group I (L5 or below) is a predictor for the absence of spinal deformity, group III (L1-L2) or IV (T12 and above) is a predictor for spinal deformity and group IV is a predictor of kyphosis. This data confirms that future spinal disorders are expected in some patients, while no spinal deformity is expected in others\[140\]. Other reports indicate that the horizontal sacrum is an indicator of the tethered spinal cord in spina bifida aperta and occulta, as signs and symptoms indicative of a tethered spinal cord appear to correspond to increases in the lumbosacral angle\[141\]. It is also reported that behavior regulation problems in children with MMC are predicted by parent psychological distress, and that more shunt-related surgeries and a history of seizures predict poorer metacognitive abilities\[142\]. It seems that adults with MMC and shunted hydrocephalus may be at risk for decreased survival\[143\].

Inadequate serum vitamin D concentrations are associated with complications of some health problems including MS, which support a possible role for vitamin D supplementation as an adjuvant therapy\[144\]. In addition, it has been suggested that the favorable effect of sunlight ascribed to an increased synthesis of vitamin D may prevent certain autoimmune diseases, particularly MS. For this reason, limited sunbathing should be publically encouraged\[145\]. It has also been suggested that altering the composition of the gut flora may affect susceptibility to experimental autoimmune encephalomyelitis, an animal model of MS\[146\]. This data could have significant implications for the prevention and treatment of autoimmune diseases. In relation to this, an interesting new proposal shows that the GI tract is a vulnerable area through which pathogens (such as H. pylori\[61\]) may influence the brain and induce MS, mainly via fast axonal transport by the afferent neurons connecting the GI tract to brain\[147\].

Symptoms such as dysphagia, impaired gastric emptying and constipation may precede the clinical diagnosis of PD by years and, in the future, these symptoms might serve as useful early indicators of the premotor stage\[81\]. Motor handicaps, such as rigor and action tremor, are independent predictors of solid gastric emptying\[148\]. It is currently recommended that the approach to PD should include strategies for detecting the disease earlier in its course and, eventually, intervening when the disease is in its nascent stage. The term Parkinson’s associated risk syndrome has been coined to describe patients at risk for developing PD. These patients may have genetic risk factors or may have subtle, early non-motor symptoms including abnormalities in olfaction, GI function, cardiac imaging, vision, behavior, and cognition\[149\].

**EMBRYOLOGICAL, MORPHOLOGICAL AND EXPERIMENTAL STUDIES AND ANIMAL MODELS**

**Embryology and morphology**

Considerable insight into both normal neural tube closure and the factors possibly disrupting this process has been reported in recent years, yet, the mechanisms by which NTD arises as well as its embryogenesis remain elusive\[150\]. Normal brain development throughout childhood and adolescence is characterized by decreased cortical thickness in the frontal regions and region-specific patterns of increased white matter myelination and volume. Subjects with MMC show reduced white matter and increased neocortical thickness in the frontal regions, suggesting that spina bifida may reflect a long-term disruption of brain development that extends far beyond the NTD in the first week of gestation\[151\]. These variations in the diffusion metrics in MMC children are suggestive of abnormal white matter development and persistent degeneration with advancing age\[152\].

In rat fetuses with retinoic acid induced MMC, the normal smooth muscle and myenteric plexus development of the rectum and normal innervations of the anal sphincters and pelvic floor suggest that MMC is not associated with a global neuromuscular alteration in development of lower GI structures\[153\]. Besides, fetal surgery for repair of MMC allows normal development of anal sphincter muscles in sheep. Histopathologically, in the external sphincter muscles, the muscle fibers were dense, while in the internal sphincter muscles, endomyssial spaces were small, myofibris were numerous, and fascicular units were larger than those in unrepaird fetal sheep\[154\]. Studies in the development of the pelvic floor muscles of murine embryos with anorectal malformations, demonstrate that the embryos show an impaired
anatomic framework of the pelvis possibly caused by neural anomalous development, whereas muscle development proceeded physiologically. These results support the hypothesis that pelvic floor muscles may function in children with anorectal malformations, in whom neural abnormalities such as MMC have been ruled out, if the surgical correction is appropriately completed. A mouse model was reported about the sharing of the same embryogenic pathway in anorectal malformations and anterior sacral MMC formation. Indeed, some of the brain malformations associated with MMC in human patients are also found in the uncorrected fetal lamb model of MMC. The late stage of gestation is important due to the presence of morphological changes. A study of in-utero topographic analysis of astrocytes and neuronal cells in the spinal cord of normal mice with MMC revealed that at day 16.5 of gestation there is a deterioration of neural tissue in MMC fetuses, mainly in the posterior region, progressing until the end of gestation with a marked loss of neurons in the entire MMC placode. This study delineated the quantitative changes in astrocytes and neurons associated with MMC development during the late stages of gestation. Data supported by other investigators show, in Curly tail/loop tail mouse fetuses, that around birth the unprotected neural tissue is progressively destroyed.

Traditionally, PD is attributed to the loss of mesencephalic dopamine-containing neurons; nonetheless, additional nuclei, such as the dorsal motor nucleus of the vagus nerve and specific central noradrenergic nuclei, are now identified as targets of PD. Early in 1988, Wakabayashi described the presence of Lewy bodies in Auerbach’s and Meissner’s plexuses of the lower esophagus, indicating that these are also involved in PD. Later on, the presence of α-synuclein immunoreactive inclusions in neurons of the submucosal Meissner plexus, whose axons project into the gastric mucosa and terminate in direct proximity to fundic glands, was reported. The authors propose that these elements could provide the first link in an uninterrupted series of susceptible neurons that extend from the enteric tract to the CNS. The existence of such an unbroken neuronal chain lends support to the hypothesis that a putative environmental pathogen capable of passing the gastric epithelial lining might induce α-synuclein misfolding and aggregation in specific cell types of the submucosal plexus and reach the brain via a consecutive series of projection neurons. A recent study aimed at characterizing the neurochemical coding of the ENS in the colon of a monkey model of PD, showed that this element induces major changes in the myenteric plexus and to a lesser extent in the submucosal plexus of monkeys. This data reinforces the observation that lesions of the ENS occur in the course of PD and that this might be related to the GI dysfunction observed in this pathology.

Experimental approaches and animal models
Animal models used in MMC include an ovine model constituted by fetal lambs, fetal sheep, a Macaca mulatta model, a mice model, and a fetal rabbit model. Several experimental approaches have been used. To study the correction of a MMC-like defect in pregnant rabbits, a spinal defect was surgically created in some of their fetuses at 23 d of gestation. The spinal defect was successfully repaired, and the fetal rabbit model was established for the study of intrauterine correction of an MMC-like defect. A new gasless fetoscopic surgery for the correction of a MMC-like defect in fetal sheep served as an alternative to current techniques used for fetal endoscopic surgery. A Macaca mulatta model was used for replicating MMC and to evaluate options for prenatal management, such as the collocation of an impermeable silicone mesh which protects the spine from amniotic liquid with results similar to skin closure. In-utero analyses of astrocytes and neuronal cells in the spinal cord of mutant mice with MMC using the curly tail/loop-tail mice model have been reported. At day 16.5 of gestation, a deterioration of neural tissue in MMC fetuses was observed mainly in the posterior region, progressing until the end of gestation with a marked loss of neurons in the entire MMC placode. These results support the current concept of placode protection through in-utero surgery for fetuses with MMC. Recently, the notion of prenatal neural stem cell delivery to the spinal cord as an adjuvant to fetal repair of spina bifida has been proposed.

The main animal model in MS was developed in mice and is called experimental autoimmune encephalomyelitis. In this experimental model, it was reported that gut flora may influence the development of experimental autoimmune encephalomyelitis, and that despite reported blood-brain barrier disruption, CNS penetration for small molecule therapeutics does not increase in MS-related animal models. The migratory potential, the differentiation pattern and long-term survival of neural precursor cells in this experimental autoimmune encephalomyelitis mice model were investigated. The results suggest that inflammation triggers migration whereas the anti-inflammatory component is a prerequisite for neural precursor cells to follow glial differentiation into myelinating oligodendrocytes. A new exciting finding with this model is that a novel regulator of leukocyte transmigration into the CNS, denominated extracellular matrix metalloproteinase inducer (EMMPRIN), indeed regulates leukocyte trafficking through increasing matrix metalloproteinase activity. Amelioration of the clinical signs of experimental autoimmune encephalomyelitis by anti-EMMPRIN antibodies was critically dependent on its administration around the period of onset of clinical signs, which is typically associated with significant influx of leukocytes into the CNS. These results identify EMMPRIN as a novel therapeutic target in MS.

Several experimental approaches in PD deal with GI issues using diverse animal models as rats, mice and primates. The advent of transgenic technologies has contributed to the development of several new mouse models, many of which recapitulate some aspects of the
disease; however, no model has been demonstrated to faithfully reproduce the full constellation of symptoms seen in human PD\textsuperscript{[77]}. As GI motility in PD has been attributed in part to peripheral neurotoxin action, rats with salsolinol induced PD were studied to evaluate its effects on intramuscular interstitial cells of Cajal, duodenal myoelectrical activity and vagal afferent activity. The results suggest a direct effect of salsolinol on both intramuscular cells of Cajal and the neuronal pathways for gastro-duodenal reflexes\textsuperscript{[18]}. Delayed gastric emptying and ENS dysfunction in the rotenone model of PD suggested that enteric inhibitory neurons may be particularly vulnerable to the effects of mitochondrial inhibition by Parkinsonian neurotoxins and provide evidence that Parkinsonian GI abnormalities can be modeled in rodents\textsuperscript{[89]}. Studies assessing the responses of myenteric neurons to structural and functional damage by neurotoxins in vivo reveal that neural responses to toxic factors are initially unique but then converge into robust axonal regeneration, whereas neurotransmitter release is both vulnerable to damage and slow to recover\textsuperscript{[173]}. The prototypical parkinsonian neurotoxin, MPTP, as a selective dopamine neuron toxin in ENS and used in a mouse model, shows loss of enteric dopaminergic neurons and changes in colon motility\textsuperscript{[173]} and its use in a primate animal model reveals changes in the myenteric plexus and, to a lesser extent, in the submucosal plexus. These models further reinforce the observation that lesions of the ENS occur in the course of PD which might be related to GI dysfunction observed in this pathology\textsuperscript{[165]}. In order to determine the changes in the dopaminergic system in the GI tract, two kinds of rodent models were used. In one, 6-hydroxydopamine was microinjected into the bilateral substantia nigra of a rat. In the other, MPTP was injected intraperitoneally into mice. The results suggest that the different alterations of dopaminergic system observed in the GI tract of the two kinds of PD models might underlie differences in GI symptoms in PD patients and might be correlated with the disease severity and disease process\textsuperscript{[174]}. In a similar rat model, it is reported that a unilateral 6-hydroxydopamine lesion of nigrostriatal dopaminergic neurons led to a marked inhibition of propulsive activity compared with sham-operated controls, suggesting that disturbed distal gut transit, reminiscent of constipation in the clinical setting, may occur as a consequence of reduced propulsive motility, likely due to an impairment of nitric oxide-mediated descending inhibition during peristalsis\textsuperscript{[89]}. Observations in Parkinsonian primates showed that when the implanted undifferentiated human neural stem cells survived, they had a functional impact as assessed quantitatively by behavioral improvement in this dopamine-deficit model\textsuperscript{[175]}. Nonmotor symptoms of PD studied in an animal model with reduced monoamine storage capacity suggests that monoamine dysfunction may contribute to many of the nonmotor symptoms of PD, and interventions aimed at restoring monoamine function may be beneficial in treating the disease\textsuperscript{[176]}. In a clinical approach, it was demonstrated that delay in gastric emptying did not differ between untreated, early-stage and treated, advanced-stage PD patients, suggesting that delayed gastric emptying may be a marker of the pre-clinical stage of PD\textsuperscript{[78]}.

**CONCLUSION**

This article reviews the current knowledge in all the fields of the neurological diseases with neurogenic bowel dysfunction, and the common issues in need of clarification. The hope is that with a full perspective of the situation, researchers can generate new ideas that can be useful for prevention, cure, or at least for the mean time, a better quality of life for the patient.

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