NONORGANIC PAIN AND VISCERAL HYPERALGESIA IN CHILDHOOD

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ABSTRACT

Visceral pain is different from the somatic one: visceral receptors have different functional engagement, the nociception degree differ from one organ to another, the few visceral afferent fibers are predominantly unmyelinised and have an extensive divergence in the central nervous system; the responses involve autonomic activation. The matrix of abdominal visceral pain, functional at birth, is overburdened by mechanical, chemical, osmotic impulses; overlapping infections or inflammation, by the released mediators create the conditions for acquiring the peripheral and central “sensibility” and the “pain memory”; behavioral and emotional factors can aggravate the visceral pain matrix hyperreactivity. In this pathogenic context it defines nonorganic pain and its severe form, visceral hyperalgesia. Genetic peculiarities influence the pain sensitivity. Based on the biopsychosocial model of functional disorders, Rome III criteria tagged the abdominal functional pain and the irritable bowel syndrome as a positive diagnosis and not a diagnosis of exclusion. Nonorganic pain, often associated with recurrent abdominal pain is among the most common medical problems encountered in pediatrics. Most patients with mild pain have a good evolution over time; a small percentage present serious and sometimes disabling symptoms. Pediatricians frequently have difficulties in delineation the diagnosis of nonorganic pain and that, sometimes, involves treatment failure. The authors present the epidemiological data, the pathophysiological mechanisms involved, the clinical approach and the therapeutic options on nonorganic pain and visceral hyperalgesia in children.

Key words: functional abdominal pain, visceral hyperalgesia, child

Visceral Pain, much different from the somatic one (skin, muscles, joints, bones) is usually difusse, bad localized (due to visceral sensory pathways poverty and the extensive divergence in the CNS); the nociception level differ from one organ to another, many viscera has receptors whose activation evokes conscious of pain perception (painless pathology in the liver, lung, kidney). (1) Due to the visceral- somatic connections, it can have a somatic reflection, visceral pain entire matrix having capacity of amplifying and involving intense autonomic and motor reactions. (2)

Visceral Nociceptors, with varying degrees of good employment, can be classified in mechanical receptors, with two types: with slow adaptation to the normal tonic contractions and distension (gastric, rectal, bladder filling, can give pain under certain conditions) and with rapid adjustment causing strong muscle contractions, painful (colonic injuries), chemical receptors (alkaline or acid resistant), thermal receptors and polymodal receptors with multiple stimulation (mechanical, chemical, thermal, osmotic). From the functional point of view, internal organs nociceptors may have a high threshold of sensitivity to natural stimuli (heart, veins, lungs and airway, esophageal, biliary, intestine, ureter, bladder, uterus), involved in acute pain,or low threshold of sensitivity (turn on natural stimuli) that encodes the magnitude of stimulus (the heart, esophagus, colon, bladder, testes) or silent nociceptors (neurons unmyelinised, dormant (receptors with high threshold, activated by inflammation and hypoxia).(1,2) Visceral afferent fibers are in most cases the axes unmyelinised fibers type C (exist, also, a few myelinised fibers), accompanying the somatic pathway to the lymph node cells on the

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dorsal sensitive nerve root, some of them borrowing the vagal pathway. Visceral sensitive fibers tackles, also, the medullar posterior horn (somatic), which explains the visceral reflected pain (pain felt in a completely different place). Diffuse (generalized) character of visceral pain is given by some viscerosensitive collaterals, which tackle also the medullar reticullar substance. Visceral information transmission follow the spinal-thalamic tract (ventroposterolateral, medial and ventroposteromedial thalamus), the spinal – solitary tract, spinal-hypothalamic tract, solitary and spinal – reticullar tract witch mediate a motor response. (3,4)

Evoked potential studies, complementary techniques of functional magnetic resonance and computed tomography by positron emission tomography have demonstrated that the visceral pain is processed in the secondary somatic – sensory cortex and very rarely in the primary one. Visceral sensation is represented in the paralimbic and limbic structures: the insular cortex, anterior and prefrontal. These areas mediate the affective and cognitive components of visceral sensitivity. The largest representation in the limbic cortex explains the visceral sensations autonomic responses which are higher than those of the somatic sensations. By magneto encephalography it been have highlighted the changes to the cortical level, associated within functional gastrointestinal pain. (5)

GENESIS AND THE PERCEPTION OF VISCERAL PAIN

1. Peripheral Sensitization: infection and inflammation of any kind, released mediators that activate the nociceptors: K and H ions, ATP, bradykinin, PG (involved in visceral hypersensitivity, with recruitment of nociceptors previously silent); is favoured the development of hypersensitivity areas in the non injured surrounding tissue; peripheral sensitization is also involved in the hyperalgesia.

2. Central Sensitization. Changes in the activity of the spinal afferent fibers are the consequence of peripheral awareness; Maintenance mechanisms are represented by N-methyl-D-asparat receptor phosphorylation expressed by the posterior horn neurons of the spine, with the modification of receptors kinetic properties that determines increased sensitivity to glutamate released from the synapses. Subsequently, excitability and field sizes of spinal neurons increase and the nociceptive and non-nociceptive impulses from adjacent tissue are amplified; Central sensitization is an important mechanism of visceral hyperalgesia. (3,4)

The brain combines the unpleasant sensations ranks with emotional and affective evocations associated with time of pain, psychological disturbances with dramatic effects on the perception of pain: anxiety attacks, depression, panic attacks, etc. Psychological variables are dependent on atentional status: awareness of family illness risk, family anxiety, implications for quality of life etc., the topographical and emotions enhanceing the activation of the anterior cingulate cortex neurons. (5)

In visceral pain is involved a high number of digestive and cerebral peptides acting as releaser and modeling agents of pain phenomenon in peripheral tissues and as neurotransmitters of nocciceptive influx in CNS: pain peptides – *bradykinin*, intestinal vasoactive polipeptid (*VIP* – related to glucagon, inhibits the digestive motility and determine vasodilatation), *P substance* (local erythema and edema occur; found also in dorsal root ganglia, posterior horn, subcortical brain barrier zones), opioid peptides sensitive to naloxon, that reproduce the effects of morphine on the digestive tract and inhibits the release of acetylcholine and P substance: enkefalines, β endorfins, and nonopioid and non sensitive analgesic peptide: neurotensin, antidiuretic hormone, bombesin. (6, 7)

Based on the biopsychosocial model of functional disorders, Rome III criteria tagged the abdominal functional pain and the irritable bowel syndrome as a positive diagnosis and not a diagnosis of exclusion. In accordance with these criteria, functional abdominal pain is defined as pain lasting more than two months, with a frequency of at least 1 episode on week and which cannot be attributed to a structural or biochemical disorder. There are four major entities, most common: functional dyspepsia, irritable bowel syndrome, abdominal migraine and abdominal functional pain, with its severe form visceral abdominal hyperalgesia. (8)

Irritable bowel syndrome (IBS): represents approximately 22-45% of functional abdominal pain in childhood. It is characterized by changes in the consistency or in the number of stools with painful symptoms improved after defecation. (9)

Typical clinical features, the underlying the diagnosis are represented by:

- 4 or more stools per day or 2 or less/week
- Constipation or diarrhea
- Frequent defecation sensation or feeling of incomplete evacuation
- Abdominal cramps or abdominal distension.

Children and adults with IBS commonly associated visceral hypersensitivity; its severity does not correlate with the severity of symptoms but can enroll in general sensory hypersensitivity. (8,9)

Pathophysiological mechanisms range from psychiatric disorders (alteration of information received at the CNS) to gastrointestinal motility abnormalities, visceral hypersensitivity, the excess production of gas, intestinal flora alteration, tampering impaired production and/or release of 5-hydroxytryptamine or other neurotransmitters. It been suggerate the existence of brain-gut interaction dysfunction, with alterations in gastrointestinal motility, secretion of the digestive tract and in the production of painful sensations. The dysfunctions are attributed to the autonomic nervous system, which comprises the sympathetic nervous system, the parasympathetic nervous system and enteric nervous system. (7,9)

Etiopathogenesis is multifactorial: post infectious (gastroenteritis with over 3 weeks duration), inflammatory (growth of T lymphocytes and mast cells in the lamina propria of the gut, increase local and systemic proinflammatory cytokines, subclinical inflammation of the intestinal mucosa is underlined by small incresased level of fecal calprotectinei in children with IBS), intestinal disbiosis (rarely, in patients with diabetes, collagen disorder or who use for long time protonic pump inhibitors), impaired regulation of 5-hydroxytryptamine production, primary CNS dysfunction, psychosomatic illnesses (anxiety, depression, panic) and last but not least genetic factors. (7)

Abdominal migraine: affects 1-4% of children being more common in girls (3:2); the average age of diagnosis is 7 years. It is characterized by paroxysmal attacks of periumbilical pain (from 1 hour to several days) that interferes with daily activities, associating 2 or more of the following symptoms: anorexia, nausea, vomiting, headache and photophobia. The diagnosis is established when in the last 12 months appear 2 or more episodes and when it have been excluded: chronic inflammatory bowel disease, surgical causes or brain tumors. It don't usually associate changes in bowel transit. The etiology and the pathophysiologic mechanisms have not been yet elucidated, possible genetic factors involved; triggers factors are represented by physically and mentally stress. (4,10)

Functional non-ulcerative dyspepsia: may affect 0,3% of the children between 0-12 years age. It is represented by persistent or recurrent pain or discomfort in the upper abdomen, events that does not improve with defecation and is not associated with changes of the intestinal transit. Nausea, vomiting and „fullness" or early satiety sensations are characteristic. From the ethiopathogenic point of view would be involved gastric motility disorders (gastric emptying delay or inappropriate gastric relaxation); *Helicobacter pylori* infection implication in not being demonstrated. (10,11)

Functional abdominal pain considered, in accordance with the Rome III criteria, a distinct entity, is not usually accompanied by alterations in bowel transit and has a different location compared to functional dyspepsia or IBS. It is continuous or episodic pain (1 episode/week), with the duration of at least 2 months; located frequently periumbilical, usually without irradiation. Diagnosis: pain present at least 25% of the time, which interferes with daily activities, associated or not with other non digestive functional disorders. (11)

Visceral abdominal hyperalgesia is severe form of functional abdominal pain, manifested as discomfort and pain associated with a normal intake of food and fluids (simple physiological functions become painful). It can be determined by postinfectious hypersensitivity (disappear in time), by subclinical pathology and/or motility disturbances (sustainable) and by visceral pain matrix components hypersensitivity (central and peripheral). It is usually associated with changes in the autonomic nervous system and intestinal motility. Modern studies have revealed the existence of gene abnormalities in pain peptides synthesis**,** individual differences in visceral sensitivity creates differences in pain perception; intervenes also the child psycho reactivity and family heritance on abdominal pain, headache, migraine. From clinically point of view, presents itself as pain triggered by food, accompanied by bloating, eructation, vomiting, transit disorders; in very severe forms even parenteral nutrition is required. The pain may be diffuse, localized: looking extensively, fricative or violent, burning, intermittent or with constant occurrence. Associated anxiety or depression, aggravated by adrenergic emotional downloads; is aggravated by infection, inflammation through other mechanisms, stressful situations. In evolution it may be associated to behavioural modifications: alcoholism or antisocial attitudes. (2,9)

The diagnosis of functional gastrointestinal diseases involve, besides exclusion of organic causes and nutritional impact assessment a series of initial assessment screening tests: complete blood count, blood inflammatory markers, hepatic tests, lipase level, serology for celiac disease, examination of urine and fecal examination (for occult bleeding or signs of inflammation markers – calprotectin or lactoferrin). Subsequently, it should be done superior digestive endoscopy, esophageal pH study, imaging studies, another malabsorption tests, psychological and neurological examination. (9)

TREATMENT

Medication is generally with no results; it been shown some variable effects of anticholinergics, tricyclic antidepressants, serotoninic antagonists, antagonists of H2 receptor. Diet – there are no benefits of low lactose diet or schemes with more fibers in the case of children with functional abdominal pain; there are no detailed studies in respect of exclusion from the diet of caffeine, fatty foods, spicy foods or carbonated drinks. Also, there are no demonstrated benefits of the administration of *Lactobacillus rhamnosus GG* (exception in IBS). Cognitive-behavioral therapy (which involve psycho education, relaxation techniques, cognitive and behavioral measures techniques) has led to a decrease in the frequency and intensity of pain after 6 months of treatment. (11,12)

Infant colic, a distinct entity of functional abdominal pain, are a frequent event, mostly under the age of 3 months. The pathogenesis is still not yet fully understood. It is known that at birth, the pain pathways are formed and the digestive tract is bombed both mechanically and chemically. There are a lot of questions involving this pathology: is there an increased solicitude of mechanic and/or chemo-receptors, there is an increased amount of catecholamine and enkephalines through the immaturity of catecholamine O transferase, is involved the cortical control immaturity or there are certain genetic characteristics.(13) Trigger factors of colic may be represented by: distention by swallowed air, over alimentation (common), excess fat in milk that slows stomach emptying, excess carbohydrates which reduces intestinal pH and increase the osmotic pressure, presence of gastro esophageal refluation, the release of pain inflammatory mediators through some immunological conflict (early sensitivity), mother anxiety, some irritants from breast milk (food additives, smoking, drugs), intestinal dismicrobism. There is no specific treatment, anti colic medication (prokinetics, absorbents, antacids); warm applications on the abdomen have low effects. (14) Digestive status and the technique of alimentation should be evaluate; breastfeeding must be maintained and it should be monitored mother diet and finally it should be developed a partnership – medical physicians- parents based on trust and friendship. In extremely severe cases, we can administer sedatives, especially in case of severe and prolonged attacks. Most colic disappear after diet diversification, but in some children the attack duration is prolonged; the anamnesis of children with functional abdominal pain, often shows the colic, remaining this question: there is a persistent defect in the visceral pain matrix or memory pain occurs? (15)

In conclusion activation of matrix components of visceral pain (peripheral and central) is expressed through a series of unpleasant sensations laced with emotional and cognitive component, (commonly associated with the autonomic system activation) in a differentiated manner of somatic pain, visceral pain may be the symptom of an organ or system disease, or may evolve as non organic suffering. The residual central and peripheral hypersensitivity (anamnesis pathology) or genetically favored, shows up individualized clinical forms of non organic pain; the severe form is expressed as visceral hyperalgesia. Ontogeny of visceral pain matrix favors the expressing of non organic pain still from the neo-natal period, influencing sustainable in some individuals the nociception threshold, the transmission and the processing and the memory brain pain; on scientific level, a lot efforts are being made for deciphering the molecular disorders of visceral functional pain to developed pharmacological means to correct this distorted system.

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