Pathophysiology of infantile colic.

M.D. Levin, MD, PhD, DSc. Radiologist,

Department of Pediatric Radiology of the 1-st State Hospital, Minsk, Belarus.

Dorot-Netanya Geriatric Medical Center, Israel.

Amnon VeTamar, 1/2, Netanya, 42202, Israel.

nivel70@hotmail.com; michael.levin@dorot.health.gov.il

https://orcid.org/0000-0001-7830-1944

https://www.anorectalmalformations.com

Scopus Author ID: 7402571390

Infantile colic (IC) is a syndrome characterized by paroxysms of irritability and inconsolable crying and screaming, accompanied by clenched fists, drawn-up legs, and a red face. It presents typically in the second or third week after birth, and peaks at 5 to 8 weeks of age; it usually resolves spontaneously by 4 months of age. The prevalence is estimated to be between 5% and 28% [1]. Rome IV criteria include all of the followings: a) paroxysms of irritability with fussing or crying that start and stop without obvious causes; b) symptoms lasting ≥3 hours a day and occur ≥3 days a week of the last week; c) absence of failure to thrive, in infants from birth to 5 months of age [2]. The IC is one of 7 functional gastrointestinal diseases (FGIDs) in infants: infant regurgitation, infant colic, functional constipation, functional diarrhea, cyclic vomiting syndrome, infant dyschezia, and infant rumination syndrome. The diagnosis of a functional disorder is, in principle, a diagnosis made by elimination of organic disease [2,3].

The cause of IC is not known. The medical hypotheses include food hypersensitivity or allergy, immaturity of gut function and dysmotility, and the behavioural hypotheses include inadequate maternal-infant interaction, anxiety in the mother and difficult infant temperament. Other hypotheses, such as hormone alterations and maternal smoking, still need confirmation, whereas the concept of alterations in the gut microflora, had been reported too [4]. There is evidence in support of three mechanisms for infantile colic which are related to the transient immaturity of intestinal functions: the enterohepatic functions and bile acid homeostasis, gastrointestinal motility, and the colonic microbiome. Some authors believe that the doctor should convince parents that there is no reason for concern, since the child's behavior normalizes by 4 months. Allegedly crying does not always reflect pain. Such an explanation releases the caregiver of the feeling of inadequacy parental care and fear for the disease [3]. Meanwhile, there is reliable evidence that in a small subset of infants with colicky behavior, a specific medical disorder such as gastroesophageal reflux [5] or milk protein allergy may be

identified [5,6]. A randomized controlled trial showed significant reductions in colic symptoms among breastfed infants whose mothers followed a low-allergen diet. Infants whose mothers excluded cow's milk, eggs, peanuts, tree nuts, wheat, soy, and fish from their diet cried less per day, compared with the control group [6]. Significant improvement was seen in the duration of crying in infants who received lactase enzyme supplement [7]. These observations may be important for understanding the pathogenesis of FGIDs and IC.

A newborn born on time with a normal weight without malformations and developing normally in the first few weeks of life he is mature for his age. During the first months of life, all organs and parts of the body grow in proportion. And only the baby's stomach grows at a faster pace in order to ensure the infant's development. This phenomenon may be important for the development of FGIDs and IC.

Purpose the present study to determining how the shape and volume of the stomach change in the first months of life, and what individual factors turn this physiological process into a painful state.

Material and methods. The article analyzes the selective radiographs of the stomach, which were made in 1985-1989 at the Byelorussian Centre of Pediatric Surgery in Minsk in 132 infants with recurrent vomiting and/ or abdominal colic. In these patients, pyloric stenosis, like other organic causes of vomiting, was excluded. At that time, we did not single out separately screaming patients. In 12 children aged 6 months - 3 years with recurrent vomiting, irritability and/or recurrent cough, in whom by X-ray and histological examinations the gastroesophageal reflux disease (GERD) was diagnosed, a manometric study of the gastroesophageal junction (GEJ) was performed. A manometric study was also performed in 10 children aged 6 months to 3 years without any gastrointestinal problems **(control group).** In 19 children aged 3 months to 4 years, a distension of the GEJ was made.

X-ray study. In the morning the child was not fed. n infants 1-3 months of age, the probe was inserted into the stomach through the mouth. The contents of the stomach were removed. If the stomach was empty, 40 ml of barium was injected, and if it was with contents, 20 ml of barium and 30 cm of air were injected. Older children drank a contrast agent from a bottle or a glass in the amount of one feeding, but not more than 200 ml. One radiograph was taken in a vertical position, and the other in a horizontal position with compression of the abdomen. X-ray diagnosis of GERD was performed according to the method described previously [8,9].

A manometric study was carried out before and after the GEJ distension in GERD patients. It was carried out by the two-channel side-holes catheter. The one hole served for the pumping of the air into the stomach, and the second hole for the measurement of the pressure. Each study was done in two stages. In the first stage the measurement hole was put into cardiac part of the stomach. Air was injected into the stomach in a volume of 50, 100 and 150 cm^3 consequently. The gastric pressure was measured throughout 1-2 sec after each inflation. In the second stage the catheter was withdrawn so as the measurement hole was located at the level of the lower esophageal sphincter (LES). The procedure was repeated in same manner and the LES pressure was monitored. The pressure in the stomach was accepted as a "zero". The results registered by the mingograph "Elema Shonander-34" through camera No-33. In patients of the control group, the resting pressure of the LES fluctuated from 3 to 7 mm Hg (4.6±0.4). The LES pressure increased after inflating air into the stomach and it was higher than gastric pressure after pumping into stomach the any amount of air in all cases. The results were analyzed statistically using the Student's t test, and the values were given as the mean ± standard deviation. Differences assumed significance at $p < 0.05$.

Gastroesophageal junction (GEJ) distension. A GEJ was expanded in infants with GERD in combination with esophagitis diagnosed by the x-ray study confirmed by histological examination of the esophageal mucous, as well as in screaming infants [10]. A Foley catheter with a guide was inserted into the stomach and 3-5 cm^3 of air was introduced into its balloon, after which the catheter was stretched out. A balloon 1-1.5 cm in diameter unhindered passes through the GEJ.

Results.

X-ray studies. The stomach had the shape of a teapot in all children of the first months of life with normal evacuation of barium from the stomach. The bulk of the contrast medium was in the body of the stomach, and the antrum was narrow in the form of a teapot spout. In these cases, the duodenal bulb was located caudal to the gastric body (Figure 1. A-B).

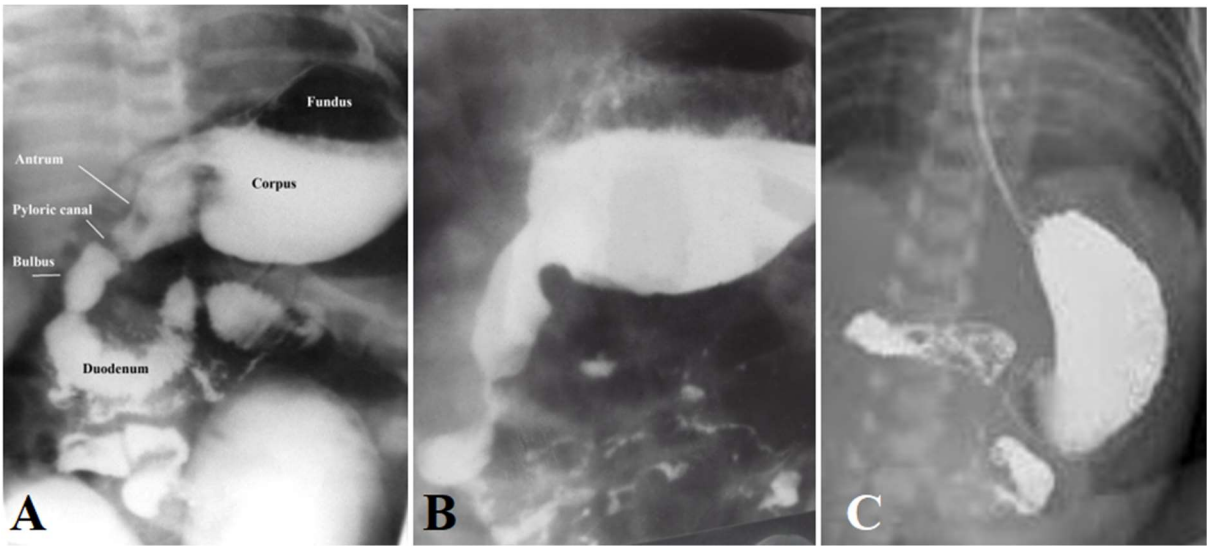

Figure 1. Radiographs of the stomach in children in the first months of life. **(AB)**. Stomach in the form of a teapot in children with good evacuation of barium from the stomach. The body of the stomach has a rounded shape and a small volume. Therefore, its lower contour is located cranial to the duodenal bulb. The narrow antrum is like the tip of a teapot. **(C)**. Infant with intestinal malrotation, which is manifested by deformation of the duodenum and scanty evacuation of barium from the stomach. The stomach is represented by a single camera, which is typical

for an adult. The distal contour of the stomach is located caudal to the duodenal bulb.

The size of the gastric shadow has always been clearly smaller in infants with the shape of a teapot.

In children with GERD, the resting pressure of the LES before distension was 0.1-6.7 (2.7+/-0.2 mm Hg). It was less than in control group ($p<0.001$). In 11 of 12 cases the LES pressure was decreased at least in one of three air inflations. After inflation of an air into the stomach the pressure in the stomach was higher than the LES pressure in all patients (**Table 1**).

Table 1. Results of the GEJ distension in 12 children with GERD.

	Resting pressure		Reaction of LES		LES/stomach Pressure	
	normal	low	raise	Drop	> 1	< 1
Before distension	4	8	1	11	-	12
After distension	7	5	9	3	8	4

Distension of the GEJ was performed in 19 patients. After this procedure, 7 children with infantile colic were sent home. In 5 cases, parents reported over the phone that after stretching, the colic completely stopped immediately after the procedure. In 4 patients over the age of 6 months significant improvement occurred. In 9 cases, there was no significant effect of GEJ distention on symptoms. Thus, in at least 5 out of 7 infants colic ceased after distension of the GEJ.

Before proceeding with the analysis of the results of this study, I need to answer two questions that inevitably will arise in my readers.

1. Why is the article devoted to a study, that was carried out thirty years ago?

After emigrating from the USSR, I could not continue to work in pediatrics. Since distension of the GEJ was also effective in adult patients with GERD, I sent my

research to the famous scientist Professor Ahmed Shafik. He with co-authors tested the short-term effect of LES distension, which he informed me in a letter. "I have had a few opportunities to work with your technique in some patients and found the results quite challenging. Have you meanwhile published your study? If yes, what is the reference on the Internet? In the negative, I wonder whether you would be interested in publishing our results together in a joint communication?" (letter attached). A study by Shafik et al was published in 2005 [11].

2. The parents gave a consent after having been fully informed about the nature of the study, the tests to be done, and their role in the diagnosis and treatment of their children. This study was approved by the Scientific Council of the Belarusian Institute for the Advancement of Doctors.

Discussion. Our data indicate, firstly, that IC is a pathological condition accompanied by severe pain. Secondly, a single distension of GEJ stops or significantly alleviates pain for a long period. In the third, after a single distension of the GEJ in some patients of different ages with GERD, a pain and other clinical symptoms of the disease are significantly relieved. In order to understand the mechanism of the long-term therapeutic effect of GEJ distension, we must understand the pathological physiology of IC.

In babies of the first months of life, two forms of the stomach were found during an X-ray examination. In some cases, the stomach resembled a teapot, and these patients had normal evacuation from the stomach. In other cases, the stomach had the same shape as in adults, but this was combined with a sharp slowdown in evacuation from the stomach and its volumes were always larger than with the shape of the teapot. Since only sick children were examined, we do not know what the stomach of healthy babies looks like. We are considering two possible options.

First option. A teapot-shaped stomach is an age norm. Obviously, a newborn's stomach volume is very small. It increases disproportionately fast as a result of wall stretching with ever-increasing volumes of food. At first, as a result of receptive relaxation, only the fundus and body of the stomach increase in volume. After 1-2 weeks, the antral part of the stomach begins to expand. It, as a result of strong peristalsis, carries out the transport of the chyme to the duodenum [12]. Gradually, the shape of the stomach takes on the form characteristic of adults. In children with impaired evacuation from the stomach, the pressure in the stomach increases rapidly, which leads to an accelerated stretching of the gastric wall and rapid appearance of the stomach shape as in adults.

The second option considers the stomach in the form of a teapot as a reaction to a pathological stimulus (food hypersensitivity, allergy etc.), which causes dyskinesia of the stomach. The narrow spout of the teapot may be due to the high tone of the antrum. An imbalance in the function of intestinal sphincters as well as intestinal hormones may be responsible of the functional gastrointestinal disorders (FGID).

Diagnostic criteria for FGIDs based on international consensus were first published in 1989. Generally, FGIDs are categorized into 7 different groups: infant regurgitation, infant colic, functional constipation, functional diarrhea, cyclic vomiting syndrome, infantile dyschezia, and infant rumination syndrome [13]. Consensus has nothing to do with science. This is a dead end that limits scientific research because of the danger of going beyond the limits of what is generally permissible. For example, the formula for the clinical diagnosis of infant colic, which is repeated almost in all articles, not only does not have any scientific justification, but contradicts common sense. If an infant with colic suffers for less than 3 weeks (Wessel's rule of threes - Rime II criteria) and according to this formula, the diagnosis of infant colic is not legitimate, does this mean that the child cannot receive treatment? And if he should receive treatment,

then what's the point in this formula? It can be agreed with Vandenplas et al that this is about symptoms, not about syndromes [13]. However, symptoms cannot be designated as functional. As syndromes they have no clear boundaries, are often combined with each other, and may be associated with recurrent abdominal pain, migraine, allergic disorder, sleep disturbance and maladaptive behavior, such as aggressiveness, later in life [14].

There is scientific evidence that food hypersensitivity plays a significant role in the pathogenesis of FGIDs, including as an IC trigger. The most common is cow's-milk allergy [4, 13, 14, 15]. It is emphasized that the allergen can pass into breast milk from foods consumed by the mother. In a study by Moravej et al. the cow's milk skin test was positive in 3 of 114 cases (2.6%) of infantile colic. All three cases recovered completely following elimination of cow's milk from the mother's diet. In the remaining cases of elimination of cow's milk from the mother's diet, there was no effect [16]. The metabolism of lactate also impacts infant gut health and may lead to acute accumulation of lactate and /or H_2 associated with pain and crying of colicky infant [17]. As shown in a randomized controlled trial, significant improvement was seen in the duration of crying in infants who received lactase enzyme supplement [18].

Cow's milk protein allergy (CMA) has a prevalence ranging from 2 to 3% [19] to 7% [20]. CMA refers to immune-mediated reactions to cow’s milk that are categorized as immunoglobulin E (IgE)-mediated, non-IgE mediated, and mixed (IgE combined with non-IgE). IgE antibodies to proteins in cow’s milk bind to mast cells, and subsequent exposure to the protein leads to mast cell degranulation and release of mediators, including histamine. Non-immune mediated reactions, such as lactose intolerance, typically lead to overestimates of prevalence CMA in population-based studies that rely on self-report [21]. CMA most frequently presents in infancy and early childhood, typically in the first 12 months of life, and tends to resolve with age [21]. Histamine acts as a neurotransmitter. It brings

about complex physiologic changes, including neurotransmission, inflammation, smooth muscle contraction, dilatation of capillaries, chemotaxis, cytokine production, and gastric acid secretion [22].

Lactose is the primary carbohydrate in cow's milk and requires an enzyme called lactase (EC 3.2.1.108) for hydrolysis. Lactase is encoded by the LCT gene, which is dominantly expressed in the small intestine. While lactase activity is high during infancy, activity diminishes after weaning in about two-thirds of the population [1,2]. However, in some populations, lactase activity is retained into adulthood, and lactose can continue to be digested in individuals carrying a heritable trait known as lactase persistence (LP). The global distribution of the LP phenotype varies in different populations, with low frequencies in people of Asian descent and high (over 75%) frequencies in some populations of European and African descent [23]. In lactase nonpersistent persons, the putative mechanisms of symptoms relate to osmotic accentuation of gastrointestinal motility and bacterial metabolism of maldigested lactose [24]. The clinical manifestations of LNP in infants are due to osmotic fluid shifts into the gut, as well as gas formation and bowel distension. This may present with abdominal pain, flatulence and diarrhea [25].

Thus, cow's milk proteins trigger allergic reactions in at least 7% of infants. The mediator of this reaction is histamine, and the digestive tract, including the stomach, in which an unusually large amount of hydrochloric acid is released, serves as a target. Other allergens that a nursing mother consumes with food act in the same way. Lactose is likely to trigger problems a significant proportion of infants with functional disorders of the digestive tract. But we do not know the mediators and their mechanisms of action on different parts of the digestive tract.

Distension of the GEJ in most infants with colic, as well as in older children with GERD, caused either an instant disappearance of the excessive crying, or a significant improvement in clinical symptoms. This is convincing evidence,

firstly, that infant colic is caused by pain, and secondly, that the cause of the pain is somehow related to the GEJ. Thirdly, it is known that the cause non-infectious pain in the abdomen, in most cases, is GERD.

Heine et al found pathological GERD in 18% of patients with persistent crying. Pathological GERD was defined as a fractional reflux time > 10% (with an esophageal pH of less than 4). Pathological GERD was more common in infants under 3 months [26]. This figure is not true, since the normal limit described in the study by Vandenplas et al [27] is erroneous. It is known that GERD can occur without typical clinical manifestations and only histological examination can identify esophagitis, which occurs as a result of the damaging effect of hydrochloric acid [28]. Regurgitation after a hearty meal is not related to GERD, as there is very little acid in the stomach contents. Fasting reflux is a picture of severe damage to the antireflux function of the GEJ. Thus, pH monitoring does not diagnose a significant amount of pathological GERD. A study by Loots et al showed that proton-pump inhibitors with left lateral position was most effective in reducing GER episodes (69 [13] to 46 [10], $P<0.001$) and esophageal acid exposure (median [interquartile range] 8.9% [3.1%-18.1%] to 1.1% [0%-4.4%], $P=0.02$ [29]. Even though PPl significantly reduced esophageal acid exposure (but not irritability) [30], some authors do not support the use of PPI to decrease infant crying and irritability [31].

Scientists unanimously reached a consensus (22/22) that "anti-acid medication are not indicated for colicky infants without manifestation of gastro-oesophageal reflux disease" [13]. With this conclusion, one can agree with the mandatory amendment that colic in infants is a manifestation of GERD.

We hypothesize that the anti-pain effect of distension the GEJ is due to the elimination of rigidity of the lower esophageal sphincter (LES). It loses elasticity as a result of esophagitis due to acid exposure. The rigid LES is not able tight to

close GEJ. After distension, the tone of the LES increases, which contributes to the cessation of acid reflux into the esophagus.

As shown by studies [3,13,29,30,31], the use of PPI does not cure GERD. Pathological reflux continues. In the phrenic ampulla acid pocket remains for a long time due to the violation of the esophageal motility, which cannot be determined with an empty stomach. Also, due to the low threshold of pain sensitivity of the esophagus, the pain does not significantly change during treatment with PPI. In some countries, the use of PPI in infants with colic is gradually increased [32,33]. This is justified, since pediatricians treat the disease, not the symptoms. Some authors believe that the doctor should reassure the parents of a screaming child, explaining that there is nothing to worry about, since the child will inevitably calm down by 4-6 months. However, acid reflux leads to irreversible changes in the esophagus and LES. Therefore, after many years, under the influence of the same triggers, the patient exacerbates a chronic recurrent gastroesophageal reflux disease.

Pathological physiology of infant colic. (Hypothesis).

In some cases, the triggers of the disease are cow's milk proteins, or other allergens that enter the stomach with mother's milk after eating food with these allergens. The mediator of an allergic reaction is histamine, which causes a sharp increase in hydrochloric acid and dyskinesia of the digestive tract. In other cases, the trigger is lactase, which accumulates in excess in the digestive tract due to the lack of lactose. Mediators of the pathological effect of lactose are not known. Changes can occur in both the small and large intestines. There is reason to believe that the same changes occur in the stomach as with an allergic reaction.

In the first weeks, the newborn consumes a small amount of milk and the stomach increases in size due to the stretching of the body and fundus of the stomach. During this period, due to the receptive relaxation of the body and the

fundus, there is no high pressure in the stomach. When the baby begins to suck greedily and the antrum of the stomach is stretched, high pressure periodically occurs in it, which leads to the casting of excess milk. The constant penetration of hydrochloric acid into the esophagus leads to esophagitis and impaired LES function. Gradually, it loses its elastic properties, which is reflected in a decrease in its antireflux function. As a result of this, even a slight increase in pressure in the stomach leads to the injection of an acidic chyme into the esophagus. Without timely treatment of GERD, an irreversible expansion of the esophagus, and shortening of the LES due to the disclosure of its abdominal part occurs.

Treatment of infant colic.

Based on the proposed hypothesis of pathological physiology and pathogenesis of infant colic, treatment should consider three directions.

1. Definition and attempt to exclude a trigger (allergy to cow's milk, lactose intolerance, allergens in mother's food).

2. Elimination of the rigidity of the LES by stretching the GEJ. This is a simple and safe procedure.

3. Conventional treatment of GERD until any of the following symptoms disappears (vomiting, poor weight, dysphagia, fussy infant, cough, putrid breath, wet pillow, anemia, night awakening to drink). Treatment includes.

a) taking PPI and antacids: b) lying on the left side and raising the head of the bed at 40°; c) frequent feeding in small portions.

After the symptoms of GERD disappear, such a child should remain under the supervision of a gastroenterologist, because GERD is a chronic progressive disease. What happened in early childhood may repeat and progress in an adult.

The division of people into children and adults is conditional. It is useful for narrow specialization. On the other hand, the connection between pediatricians

and their patients who have crossed the 18-year mark is lost. An example is excerpts from Leung and Hon's article "Gastroesophageal reflux in children: an updated review" [34]: a) Regurgitation is the most frequent symptom of gastroesophageal reflux and is present in nearly all cases (?); b) In the majority of cases, no treatment is necessary for gastroesophageal reflux apart from reassurance of the benign nature of the condition (?); c) this condition is benign and self-limiting (?).

A consensus survey is a policy tool. It is not used as an instrument of scientific knowledge in any of the fields of science.

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