

New insights on the pathogenesis of pyloric stenosis of infancy. A review with emphasis on the hyperacidity theory*

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ABSTRACT

A review is presented on the theories concerning the cause of pyloric stenosis with emphasis on the primary position of inherited hyperacidity in pathogenesis. Existing theories are critically analysed and the hyperacidity theory is precisely defined in the light of recent physiological insights into the gastrointestinal hormone motilin. The progressive fixed fasting hypergastrinaemia within the first few weeks of life will, in the baby who inherits acid secretion at the top of the normal range, produce hyperacidity of sufficient severity to trigger the process of acid-induced work hypertrophy of the pylorus. The potential contribution of motilin is discussed. The baby who inherits a normal gastric acidity will not reach acid levels severe enough to trigger sphincter hypertrophy despite the early gastrin stimulus. The potential threat will cease when gastrin naturally declines with age and the pyloric canal becomes wider. Genetic factors clearly must also be involved and these are separately discussed.

Keywords: Infantile Hypertrophic Pyloric stenosis (IHPS); Immunohistochemistry; Smooth Muscle Cells; Gastrin; Motilin; Gastrointestinal Motility; Erythromycin; Pyloromyotomy; Acidification of the Stomach; Pyloric Sphincter Function; Receptor Binding; Pathogenesis; Antral Motility; Gastric Outflow Obstruction; Linkage Analysis; Single Nucleotide Polymorphism; Interstitial Cells of Cahal; Nitric Oxide Synthetase

1. OVERVIEW

There can be few clinical conditions more fascinating and less understood than hypertrophic pyloric stenosis of infancy (IHPS). It is the most common cause of upper gastro-intestinal obstruction in the neonatal period.

Any theory of cause clearly requires to explain and be consistent with the extraordinary clinical features.

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Four main theories of causation have emerged.

- 1) Immunohistochemical abnormalities.
- 2) Genetic abnormalities.
- 3) An infectious cause.
- 4) The hyperacidity theory.

2. IMMUNOHISTOCHEMICAL ABNORMALITIES

It is accepted that the sphincter muscle abnormality consists of both hyperplasia and hypertrophy of the circular muscle fibres [1].

2.1. Local Growth Factors and Mechanisms

Histo-chemical techniques have suggested that growth proteins and other factors are increased within the sphincter muscle. Increased sphincter levels of insulin-like growth factor (IGF), platelet-derived growth factor (PDGF) [2] and growth signalling pathways [3] as well as other growth indicators [4] have been recorded by the same principal investigator.

The significance of these findings is much reduced because

- 1) Control sphincter specimens were harvested variable hours after death.
- 2) Only qualitative findings were reported in so far as no allowance was made for the greatly increased contribution from smooth sphincter muscle in IHPS.
- 3) Smooth muscle hypertrophy for any reason such as work hypertrophy has been shown depend upon the accumulation of local growth factors probably produced by the smooth muscles themselves [5-7].

Thus, there are as yet no reliable evidences of a primary abnormality in local growth factors in the pathogenesis of IHPS.

2.2. Neural and Neuro-Transmitter Abnormalities

Selective reduction of intra-muscular nerve supporting cells [8]; neural cell adhesion molecules [9]; cholinergic innervation [10] and neurotrophins [11] have also been reported.

The comparative controls again relied on post-mortem normal sphincters hours after death and the studies were again qualitative. Hence the contribution of nerve fibres to the slide image is likely to have been skewed by the increased smooth muscle mass in the pyloric tumour specimens.

Others have reported on qualitative analysis of myenteric plexus nerves which are described as longer or thicker with shorter nerves in the longitudinal layer in the human pylorus. There was, in addition, a reduced expression of muscle-relaxing neurotransmitters such as nitric oxide synthetase and vasoactive intestinal peptide [12].

Some breeds of dogs also suffer from what appears to be canine IHPS [13].

When quantitative histological analysis is attempted using computer-assisted analysis with post-mortem normal controls, there was no change in the innervation of the pylorus compared to the reported changes above in the human pylorus [14]. Immunohistochemistry revealed that nitric oxide synthetase was expressed normally as was substance p (a tachykinin). Only vasoactive intestinal polypeptide (VIP) was shown to be reduced compared with the normal post-mortem canine pylorus [14].

The interstitial cells of Cahal (ICC) react with heme-oxygenase 2 (HO) to locally release carbon monoxide—a gaseous neurotransmitter which relaxes smooth muscle. Both HO and ICC were found to be deficient or absent in the full thickness biopsies from 15 pyloric tumours. The 8 controls who were not well matched (age range 1 day to 5 years) had no gastro-intestinal disease and were presumably autopsy controls but this is not stated [15]. The ICC cells are thought to mediate in inhibitory effects on the pyloric and oesophageal sphincters. [16] and a decrease has been reported in several disorders of gastro-intestinal motility [17] including IHPS [18] The intra-muscular ICC cell has also been thought to play a part in the nitric oxide dependant inhibitory mechanism which inhibits the pyloric sphincter [16].

There are so many observed abnormalities that it is unlikely that anyone of them is a prime mover in pathogenesis. Most reported abnormalities are uncertain since post-mortem sphincters controls have been used as controls and few have attempted quantification. Moreover, the abnormalities, if correct, may simply be the mechanism by which a sphincter becomes hypertrophic as a result of frequent contraction.

3. THE GENETIC CONTRIBUTION

The well-documented prevalence in high-risk families and the increased incidence among siblings testify to an inherited component. A multifactorial sex-modified threshold method of inheritance has been proposed which satisfies the known inheritance patterns [19].

Syndrome and monogenic forms exist [20,21] as well as chromosomal abnormalities including translocation of chromosome 8 and 17 and a partial trisomy of chromosome 9 [22,23]. Autosomal-dominant monogenic forms have also been reported [24,25].

A locus for monogenic IHPS susceptibility has been identified at 16p13-p12 on linkage analysis [26] and also on 16q24 [27]. and a genetic heterogeneity is thought likely [26]. The gene on chromosome 12q which encodes for the enzyme which produces the muscle relaxant nitric oxide (neuronal NO synthetase) is considered also to have a role [28,29].

A more recent study using Single Nucleotide Polymorphism (SNP) based linkage analysis has been reported. 81 pedigree families with IHPS were investigated. Non-parametric and parametric analysis identified loci on chromosomes 11q14-q22 and Xq23. These two linked regions contain functional candidate genes which belong to the Transient Receptor Potential genes (TRPC) which have a possible role in smooth muscle control and hypertrophy [30]. The authors concede however that an environmental factor—as yet unknown—is also clearly implicated and is required.

They also concede that the common form of IHPS is inherited as a complex multi-factorial trait.

One consequently should not be surprised to find that the concordance rate in monozygotic twins (0.25 - 0.44) while higher than in dizygotic twins, nevertheless is much less than unity [31].

Neither the genetic nor the immunohistochemical theories address the curious clinical and important time-sensitive features of this condition. The acceptance of a genetic heterogeneity is in agreement with the multifactorial sex-modified threshold pattern of inheritance.

A genetic theory based on TRPC stimulus to smooth muscle growth would not explain the long-term cure by pyloromyotomy.

4. THE INFECTION THEORY

The search for a time-sensitive precipitant and the need to discover the environmental factor in pathogenesis has led to speculation about a self-limiting infection.

Pyloric babies have been investigated by examining throat swabs and comparing them with normal controls. There was no difference when the common naso-pharyngeal viral pathogens were analysed [32].

Helicobacter pylori (H Pylori) the important gastric pathogen and known stimulant of gastric acid secretion [33] has also been investigated.

H. Pylori is known to be present in babies from 6 months in age. In a 5 year follow-up study of mother and child random amplified polymorphic DNA fingerprinting has revealed that mother to baby transmission does occur [34].

In another study prompted by an index case suspicion of H. Pylori organisms on histology, 16 consecutive babies with IHPS underwent gastric biopsy pre-operatively. All the urease tests were negative; there were 4 cases of chronic gastritis; 6 of mild gastritis and 5 with normal histology. No H. Pylori were discovered on histology. [35]. At the age of pyloric presentation immunological tests for H. Pylori are unreliable since maternal transmitted immunity may last up to 6 months.

A further study using stool culture for H Pylori in 39 consecutive babies with IHPS failed to discover a single case. Control babies were also negative [36].

Curiously the major consequence of H. Pylori infestation in adults—namely hyperacidity—is not mentioned as a possible link between infection and the development of IHPS in any of the cited papers.

In the absence of a known cause the gastritis recorded on biopsy presumably would simply be a consequence of prolonged gastric stasis.

There is consequently no evidence at present to support an infectious cause.

5. REQUIREMENTS FOR ANY THEORY OF CAUSE

Any acceptable theory of cause would naturally require to explain

- 1) The male/female ratio of 4/1 [37].
- 2) The rapid disappearance of the tumour and long-term cure after pyloromyotomy [38].
- 3) The persistence of the tumour after gastroenterostomy [39].
- 4) The absence of the tumour at birth and the presence of the tumour at around 4 weeks of age [40].
- 5) The known positive influence of a family history [41].
- 6) The finding of high acid secretion in babies with IHPS and an increased incidence of duodenal ulcer dyspepsia and high volume outputs in long term survivors [42].
- 7) An increased incidence with erythromycin therapy, an antibiotic which increases antral and pyloric contraction [43,44].

An excellent contemporary review of the clinical and epidemiological features of this condition may be obtained by consulting a review by MacMahon [45].

There are in addition two requirements which need to be addressed by any theory of causation.

- 1) A temporary developmental factor

Any condition which presents within a narrow age range of 4 weeks and which goes away and does not return (if the baby is kept alive by standard medical treatment) is likely to be caused by developmental and time-sensitive factors.

In other words, a mechanism must come into play at around 4 weeks of age which is of a temporary nature.

- 2) A sphincter factor

Any condition which is cured by dividing a sphincter is likely to be caused by the contraction of that sphincter. This is especially true when the hypertrophied sphincter disappears within a matter of weeks. Thus, it is to be expected that the tumour will persist after gastroenterostomy and it does [39].

6. THE HYPERACIDITY THEORY

A theory is proposed which does satisfy all the known clinical features and is also consistent with the additional two requirements.

The theory is based on the inheritance of an acid-secreting ability—possibly a parietal cell mass—at the top of the normal range and the consequence of hyperacidity on sphincter function.

If fasting gastric acidity is simply assessed by measuring the pH there is little difference between IHPS babies and matched controls although recorded pH levels tend to be lower [46]. The pH logarithmic scale would require a huge difference in H⁺ ions before statistical significance is reached.

However, when the stomach is emptied and basal acid secretion is measured, untreated babies with PS secrete much more acid than matched controls. Indeed, the difference is huge [47].

When histamine stimulated acid secretion is measured 7 days after successful pyloromyotomy, the pre-operative hypersecretion of acid is maintained [48]. Thus the acid hypersecretion is real and is not due to failure of the acid to leave the stomach.

Supporting evidence for the assertion that hyperacidity is the prime mover in pathogenesis is as follows:

- 1) Medical treatment with gastric wash-outs; cautious underfeeding and precise body-weight titrated atropine therapy produce long term cure rates similar to surgical cure. The seminal paper by Jacoby in which 200 babies were randomly allocated to receive medical or surgical treatment. Jacoby performed both surgery and the medical treatment. The mortality was approximately 1% in both groups of 100 babies and there were no recurrences [49].

The components of medical treatment all reduce gastric acidity for the temporary period during which treatment is given.

- 2) Any baby in the pyloric age group who persistently vomits and who is alkalotic, is invariably found to have IHPS [50]. That is, there is more acid lost from babies with IHPS than from controls.

- 3) The notable experiments of Prof. Dodge in 1976 revealed that 25% of new born puppy dogs, developed

pyloric stenosis (PS) indistinguishable from IHPS when pentagastrin injections were given before labour to their mothers [51]. Even more puppies developed PS when pentagastrin injections were given to them after birth and 16% displayed superficial mucosal ulceration of the pyloric mucosae [51]. It has now been established that gastrin crosses the placental barrier of dogs to cause gastric acid secretion in the foetus [52].

4) Pyloric stenosis shares the same male/female sex ratio as duodenal ulcer in adults, a condition known to be due to hyperacidity.

Hence it is reasonable to suppose that hypersecretion of acid is fundamental to the pathogenesis.

It is of particular interest in this regard to note the report that pre-term normal male babies produce more acid than female babies, during the first 10 days of life [53]. This finding remains unchallenged.

If it is true the male predominance, according to this theory, would be explained.

More supporting evidence for hyperacidity in pathogenesis comes from the observation by Dodge of a preponderance of Group O blood group in babies with IHPS [54]—a preponderance shared by patients known to suffer from duodenal ulcer [55].

6.1. The Consequences of Hyperacidity on the Pyloric Sphincter

The most potent cause of pyloric muscle contraction in dogs is the entry of acid into the duodenum [56,57].

When intravenous pentagastrin is given to adults, the first consequence is pyloric delay (presumably from pyloric contraction) [58].

In adults with hyperacid disease, the early symptom of post-prandial bloating (pyloric delay), is quickly relieved when acid secretion is abolished by timely antacid therapy. Indeed, selected cases of pyloric stenosis in adults may be successfully managed by antacid therapy [59].

On a longer term view, why should simple division of the sphincter so regularly produce a complete cure for all time—if the repeated contraction of a competent sphincter is not part of the pathogenetic process? Simple division would produce only a temporary mechanical solution if the pathogenesis involved pyloric muscle hyperplasia from genetic abnormalities controlling smooth muscle growth or from the primary inappropriate accumulation of local growth factors.

Hence a competent sphincter—freely able to contract must be integral to the pathogenesis.

6.2. The Consequences of Repeated Pyloric Contraction

There is no reason to suppose that the pyloric circular muscle differs from muscles elsewhere. Consequently,

with repeated acid-induced contraction, it will undergo hypertrophy and hyperplasia mediated by local growth factors (The first mention of work-hypertrophy as a potential cause occurred in 1921 but it was dismissed presumably because of an absence of a known-sphincter-stimulating factor) [60].

Work hypertrophy within the first few weeks is likely to be further enhanced by the high plasma levels of the trophic gastro-intestinal hormone gastrin known to be present in increasingly high levels within the first 4 weeks of life. In normal babies fasting gastrin levels rise steeply within a few days of birth to reach levels much greater than the usual levels recorded in adults even after food [61,62].

Feeding is an obvious stimulus to sphincter contraction.

All clinicians will have witnessed the food stimulated regular contraction of the hypertrophied sphincter during a test feed.

Post-delivery enteral feeding is thought necessary for the usual development of IHPS and also is required for the development of neonatal hypergastrinaemia [62].

The first-born baby who vomits is likely to be immediately put back on the breast by an anxious first-time mother thus facilitating the process of hypertrophy and explaining the phenomenon of primogeniture.

The experienced mother probably (and wisely) will give the stomach a rest.

The low incidence of PS countries such as Africa and Asia where undernutrition is common may be explained by relative underfeeding and a reduced frequency of sphincter contraction [63].

A 7-fold increase in the incidence of IHPS has been reported among newborn infants who had received erythromycin in antibiotic doses for post-exposure pertussis prophylaxis [44].

Erythromycin, a macrolide antibiotic, specifically increases antral motility [64] and contraction of the pyloric bulb [65,66] by binding to motilin receptors. These receptors not only exist in cholinergic nerves but also are thought to exist directly on smooth muscle. The strongest antral contractions induced by large doses of erythromycin are not blocked by atropine and direct muscle stimulation is likely [67]. Indeed the authors of the pertussis report [44] speculate that that the marked increase of gastric motility may cause (work) hypertrophy of the pylorus.

Motilin enhances intestinal contractions and the receptors are not functional before 32 weeks of gestation or at birth and may develop at around the time presentation of IHPS [67].

It is of course of great interest to know how the release of motilin relates to the hyperacid theory of IHPS.

Despite the original finding that duodenal alkalinisa-

tion releases motilin [68] further enquiries have shown that duodenal pH does not influence endogenous motilin release if the pH is between 2 and 8.5 [69] and that the presence of nutrient in the duodenum strongly suppresses the typical pulsed interdigestive motilin release [70,71].

Hence the empty duodenum in IHPS may provide a means whereby motilin maintains the stimulus to pyloric sphincter contraction.

Even more intriguing is the finding from Bloom's group that duodenal acidification releases motilin [72]. Hence the primary pyloric contraction from acid stimulation may also be motilin related.

The voltage-tension curves for the antral-pyloric region coupled with the narrow pyloric diameter mean that the interdigestive phase 2 *first* contractions will regularly encounter a closed pylorus consistent with sieving function of phase 2 contractions [73].

Studies in adult with an active duodenal ulcer (and presumed hyperacidity) have shown that Phase 2 gastric contractions-rhythmic and phase locked but not expulsive occur in the inter-digestive phase. Phase 111 contractions which empty the stomach require acid-blocking drugs to alkalinise the antral contents [74,75]. The fed-pattern contractions will also increasingly meet with a closed pylorus as the condition develops.

Hence the baby with uncontrolled high gastric acidity is vulnerable to regular continuous antro-pyloric contractions with little opportunity for loss of acid through gastric emptying. Given that the acid stimulus acid will be retained, this situation will be conducive to work hypertrophy.

It is of further interest to record that motilin plasma levels rise steeply after birth in normal infants reaching levels greater than those in fasting adults by day 24. These high levels only occur in the fed baby [62].

There is one report of low levels of plasma motilin in IHPS [76] and these studies need further corroboration.

An analysis of the motilin gene (MLN) has compared normal controls with babies with IHPS and no mutations or differences have been detected [77].

6.3. The Consequences of a Stenosed or Obstructed Pylorus on Acid Secretion

Adults with pyloric stenosis are known to secrete more basal acid and meat-stimulated acid than those with non-obstructing duodenal ulcers [78,79] and gastric hyperplasia has been shown to follow artificial duodenal obstruction in rats [80].

When the pylorus is artificially narrowed in rats, acid secretion (and meal-stimulated gastrin secretion) is increased [81].

In addition a pyloro-oxyntic autonomic nerve reflex for increasing acid secretion in response to antral distension has been shown to exist in dogs [82].

Thus when early pyloric stenosis begins and outlet obstruction occurs, a further acid stimulus is triggered by many different factors and the process becomes self-perpetuating.

A recent decline in the incidence of IHPS that parallels the decline of sudden infant death (SIDS) has been observed in Sweden, coinciding with the implementation of the "back to sleep campaign" [83]. Gastric emptying is likely to be reduced in the prone position given that the second part of the duodenum will require to empty against gravity. Thus the improved gastric emptying in the supine position may explain the reduced incidence.

6.4. The Developmental Factor

In adults there is a negative feedback between antral acidity and plasma gastrin. Thus acid secretion is normally under a control mechanism in which dangerous hyperacidity is avoided because gastrin secretion is switched off [84].

A rising gastrin and rising acid e.g. Zollinger Ellison (ZE) syndrome means that gastrin would be presumed to be the primary cause of the acid secretion and the negative feed-back is consequently ineffective. With ZE syndrome, maximal gastrin secretion is inferred by the absence of any further post-prandial gastrin increase.

Histamine-stimulated acid secretion has been assessed in normal babies from 12 hours to 3 months of age. Acid output rose gradually to a peak at around 3 weeks of age. Males and female babies were not separately assessed [85].

The observation of the greatest interest is that fasting gastrin levels are also rising during the first 2 - 3 weeks of life and do not begin to fall until 6 weeks of age [61, 86,87]. One possible explanation is that the negative feed-back is ineffective or immature at this time.

There are indeed reports which suggest that this is true.

When fasting gastrins are high at around 60 hours of age, there is no post-prandial gastrin response. At around 3 weeks of age the fasting gastrins are a little lower and a post-prandial gastrin response can be detected [88].

The authors also explain these findings on the basis of a relative insensitivity of the gastrin-acid relationship. By this they mean it has not matured sufficiently to respond inversely to antral acidity. The rising gastrin in the enterally fed baby is thought to stimulate gut hypertrophy and act in addition as a gastro-intestinal trophic agent [89].

Hence the 2 - 3 week normal baby exhibits some of the biochemical findings of a temporary ZE state.

Earlier proposal that simply elevated plasma gastrin may be primarily driving the hyperacidity in IHPS [90] have generally not been supported by fasting or post-prandial gastrin measurements [89-91]. One would ex-

pect lower fasting gastrins in the hyperacid pyloric baby and their normality may indicate a relative elevation.

Thus the baby who inherits a capacity to produce acid secretion at the top of the range (perhaps due to an inherited supernormal parietal cell mass) is especially vulnerable to uncontrolled hyperacidity in the first 3 weeks of age. There is no negative feed-back control.

Consequently repeated acid-provoked pyloric sphincter contraction will lead naturally to pyloric work hypertrophy of the sphincter muscle with IHPS as the natural outcome.

The Primary Hyperacidity Theory explains all the classical and less well known clinical observations.

It explains the male predominance—the self-cure with time—the typical presentation at 4 weeks of age—the familial (genetic) inheritance and the increased incidence of hyperacid disease in adulthood. It also may explain the increased incidence in oesophageal atresia when alkalinising amniotic fluid may not enter the stomach and hyperacidity is relatively unchecked both before and immediately after birth [92].

It explains the complete cure by sphincter division and the good response to antacid measures which result from standard medical treatment at the critical time.

Hyperacidity occurring at beyond the classical 4 - 6 weeks age of presentation is unlikely to produce the typical tumour since the negative feedback will have become established and the normal pyloric widening with age will also make critical pyloric obstruction less likely.

The occasional phenomenon of IHPS which appears to change vary from day to day is also consistent with the Hyperacidity theory as here presented. The degree of outlet obstruction is a dynamic process in these babies with the improving consequences of the passage of time in a changing balance with the deteriorating food-related process of work hypertrophy.

7. CONCLUSIONS

The genetic theories while clearly meaningful and essential can not stand on their own. The poor concordance in monozygotic twins needs to be explained. Why potential smooth muscle stimulators (TRPC) should confine themselves to the pyloric sphincter is also not explained.

Genetic abnormalities may contribute in two ways.

1) By facilitating sphincter hypertrophy through growth factors such as TRPC acting on a sphincter which is being primarily stimulated by hyperacidity.

2) By producing constitutional hyperacidity in the neonate through a heterogeneity multifactorial mechanism.

The histochemical theories suffer from problems related to adequate control specimens. They do not explain the time issues. If accurate the changes may simply reflect the process by which work hypertrophy occurs.

The infectious agent theories satisfy the need for a self-limiting precipitant but so far have only produced negative results.

It is clear that an environmental factor is necessary to explain the time-sensitive aspects of IHPS. The hyperacidity theory here presented satisfies all the clinical observations including the time-sensitive presentation.

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ABBREVIATIONS

IHPS: Idiopathic hypertrophic pyloric stenosis of infancy.

ICC: Interstitial cells of Cahal.

IGF: Insulin like growth factor.

PDGF: platelet derived growth factor.

Sp: Substance P.

VIP: vasoactive intestinal polypeptide.

Haem: oxygenase 2(HO).

ZE syndrome: Zollinger-Ellison Syndrome.