The Cause of Pyloric Stenosis of Infancy? -A View from the Sidelines

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Abstract

Pyloric stenosis of infancy (PS) has been known to exist for more than 100 years. The acknowledged clinical features are extremely curious and not in dispute. The cause remains unknown despite an increase in recent years of several theories. The characteristic pyloric“tumour”has been shown to be due to hyperplasia and hypertrophy of the sphincter muscle. Spontaneous long-term cure may occur if the baby survives beyond the first 3 months. Temporary medical treatment with antispasmodics such as atropine, gastric washouts and cautious underfeeding produce long-term cure rates of well over 95% although in modern practice the classical pyloromyotomy has now become almost mortality free.

In 1903 Freund an early observer of this condition declared that hyperacidity was the cause [1]. Despite the known potent effect of intra-duodenal acid in causing sphincter contraction this theory has never (until now) been put to the test. Nitric oxide (NO) relaxes mammalian gut smooth muscle and an absence of nitric oxide synthase(NOS), the chemical that locally creates NO, has been reported to cause contraction and outlet obstruction. Other recent theories which include an abnormal concentration of growth factors in the sphincter muscle: a primary genetic cause and an acid-producing helicobacter gastritis have all largely been discounted. None of these theories attempt to explain the clinical features.

The constitutional hyperacidity theory (Freunds theory) has at last been well studied. It can explain all the clinical features. It is presented here as the true cause.

Keywords: Pyloric Stenosis of Infancy; Aetiology; Neonatal Hypergastrinaemia; Neonatal Hyperacidity; PPI Drugs

What is the Cause of Pyloric Stenosis of Infancy? -A View from the Sidelines

All medical practitioners will be familiar with the aphorism-listen to the patient; he is telling you the diagnosis. The baby with PS however vocal, cannot speak. The language he uses is confined to the many curious clinical clues associated with PS. The medical and surgical establishment have failed despite 100 years of observation, to unlock the puzzle- to discover a believable cause. This failure is understandable. What is less easy to understand is the failure to attempt to fit the theories to the clinical facts.

In an important paper from 1921 Dr. John Thomson of the Royal Infirmary, Edinburgh reviewed 100 cases from 1894 - 1919. The mortality of patients treated either surgically or medically in public hospitals was a staggering 75%. He also observed that the pyloric swelling was due to circular muscle hypertrophy and that the disease may self-cure provided the baby survived long enough without treatment. When feeds were restricted and gastric washouts employed, the baby improved. He also identified three categories of PS.

1. An acute form.
2. An ordinary form.
3. A very mild case. These he described as not at all uncommon often resolving completely simply by dietary restriction alone.

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He also debated whether the pyloric swelling was a real tumour (a redundancy of growth) or due to constantly recurring over action of function-(work hypertrophy). He favoured work hypertrophy [2].

Over the ensuing years other clinical facts began to gradually emerge. The male preponderance of 5/1; the onset of projectile non-bilious vomiting at around 4 weeks; the greater frequency in first-born babies; the family history in 25% of babies and the increased frequency of hyperacidity problems in adult life. Other more subtle associations included the increased incidence when a motilin agonist (erythromycin) was used to prevent or treat whooping cough in infants [3] of the right age. Little is yet known about what dose or duration of erythromycin is required to trigger the development of PS.

PS is always the cause whenever a vomiting baby at this age became alkalotic [4]- an indication that PS babies are losing more acid when they vomit. An increase in frequency of PS has also been reported in babies with trachea-oesophageal fistulae (TOF) [5]. With most of these babies the alkaline liquor amni is unable to reach the stomach and they emerge into life with stomach contents more acidic than normal. They have a head-start!

Indeed much of the recent literature in our generation is often simply a repetition of already known facts (here we go again) or the supposed new associations with other diseases.

The better-known of recent theories, none of which seek to explain the clinical facts, are as follows:

Sphincter concentrations of chemicals of interest

All of these studies in which a small slice of sphincter muscle is removed during pyloromyotomy, are bedevilled by the impossibility of ethically obtaining matched infant control tissue.

Nitric Oxide Theory

Nitric oxide (NO) is a powerful relaxer of gastro-intestinal smooth muscle. It is present in the endothelium of mammalian arteries but also in the enteric nerves with supply mammalian smooth muscle. Nitric oxide synthase, (NOS) the chemical which locally produces NO was not seen in 9 circular sphincter muscles from PS neonates but was present in 3 allegedly control neonates some hours after death and also in 4 children whose ages ranged up to 13 years of life [6]. Clearly these controls were unsatisfactory.

This paper led to the supposition that the absence of NO and the subsequent failure of the sphincter to relax, led to sphincter hypertrophy. There was no attempt made in this study to allow for the effect of the huge difference in the volume and nature of the PS sphincter muscle and of course there were truly no adequate controls. It is entirely possible that a repeatedly contracting sphincter which produces work hypertrophy does so by selectively reducing the supply of the relaxing factor to the sphincter. A reduced concentration of NOS may be secondary to the process of work hypertrophy. Such a phenomenon would be consistent with the curious finding of normal concentrations of NOS after pyloromyotomy [7]. Other studies have found that NOS is absent only in a subset of PS neonates [8].

The NOS gene has been disrupted in mice. The mutant mice developed sphincter hypertrophy and large stomachs [9]. The associated and necessary hypertrophy of other smooth muscles is not seen in the human neonate with PS.

Despite this finding, the restoration of NOS in the circular sphincter muscle after pyloromyotomy; the need to explain a relevant genetic abnormality all combine to make the NO story difficult to accept.

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Growth Factors

Other papers with the same flawed controls have similarly alleged that local growth factors appear in enhanced concentrations in PS sphincter muscle [10,11]. Any muscle which enlarges due to repeated contraction does so by attracting growth factors [12]. Their presence signifies only that the muscle is growing—nothing more. Consequently there is no evidence that these growth factors, if they do really accumulate, signify anything other than work hypertrophy.

Genetic Factors

The concordance rate in monozygotic twins while greater than in dizygotes, is still only between 0.25 and 0.44 [13]. This observation clearly means that environmental factors e.g. a different feeding regime must be necessary. Extensive study of the genome in PS has not revealed any single associated abnormality [14,15]. A multigenic and multifactorial inheritance— the way in which constitutional hyperacidity is presumed to be inherited, is most likely.

Neonatal Infection

Throat swab analyses of the common nasopharyngeal viruses showed no difference between PS babies and controls [16].

Similarly there is no evidence that a temporary infestation with Helicobacter Pylori has any part to play despite the clear possibility that temporary hyperacidity may be caused [17].

The Hyperacidity Theory

The beginnings of this theory evolved directly from the observation that in normal development, neonatal fasting gastrin and gastric acidity rises progressively in the first few days and weeks after birth. This neonatal hypergastrinaemia exceeds fasting adult levels [18]. There is no further gastrin increase after a feed. This strongly suggests that this early gastrin secretion is not under negative feed-back control. It is maximally stimulated and is acting physiologically like a gastrinoma (Zollinger-Ellison syndrome) [19].

Unsurprisingly gastric acidity during this time also rises and reaches a peak around 2-3 weeks before slowly falling (Figure 1) [20]. When the negative-feed-back matures in later weeks, fasting gastrin falls and, for the first time, a post-feed increase in gastrin is recorded [21,22].

Figure 1: (After Agunod). All parameters of gastric function, acid, intrinsic factor and pepsin peak at around 14 - 17 days after birth.

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Other observations which confirm maximal gastrin secretion are:

1. Up until 2 months of age the usual post-feed increase in gastrin does not occur. It is already maximally stimulated [21].
2. In the first and second days of life there is little difference between the basal acid secretion and penta-gastrin stimulated maximal acid output [23].

With normal babies this peak developmental hyperacidity is of little significance. It simply reduces the chances of an early enteric infection. However the baby who inherits a greater parietal cell mass, with constitutional hyperacidity, is in a different category. Their developmental peak acidity will be dangerously high. Acid entering the duodenum is the most potent way to contract the pyloric sphincter [24,25]. Repeated acid stimulation will cause repeated sphincter contraction and progressive sphincter hypertrophy. When gastric outlet obstruction occurs further acid secretion occurs [26,27] and the stage is set for a fatal outcome.

Continued inappropriate attempts to feed her vomiting child-most probably from an inexperienced first time mother- only aggravates the condition by provoking post-feeding sphincter contraction. This phenomenon is clearly illustrated in the classical diagnostic test-feed and by reference to the difference between feed provoked sphincter contractions and the contractions when the stomach is empty (Figure 2) [28] 52 years later.

![Figure 2: (With permission from M. Schemann) The graph shows that in dogs pyloric contractions in frequency and amplitude are greatest after a feed. The classical test feed in PS demonstrates this phenomenon well.](image)

Gastric washouts and cautious underfeeding with atropine (to reduce vagal acid secretion) may save the day. Intravenous cimetidine for a short time is even better. In early cases of PS with sphincter diameter of 3 mm. or less, long term cure is achieved in 16 out of 17 babies (Baniegbhal, Personal Communication).
Pyloromyotomy, of course is a wonderfully effective treatment which provides an instant long-term cure. The now incompetent sphincter has a wider lumen. Further work hypertrophy is impossible and acidity naturally falls when the negative feedback is established. The no sphincter-no tumour situation is yet another indicator that sphincter work hypertrophy is the cause of PS. When gastroenterostomy was formerly used the patient survived but the tumour persisted for 52 years [29].

How the primary hyperacidity theory explains the clinical features

Are babies with PS hyperacid?

Measuring the fasting pH of stomach contents is a poor way of comparing the acidity of PS babies with normal controls. It is a logarithmic scale and will only separate hugely different acidities. However when basal acid secretion rates are compared PS babies have a much greater acid secretion [30]. More importantly, after successful pyloromyotomy this hyperacidity persists [31]. Hence retained acid is not the explanation. The hyperacidity is constitutional. Long term studies reveal what you expect-an increased incidence of problems with hyperacidity in later life [32].

All vomiting babies in the pyloric age who become alkalotic will, without exception, have PS [4]. They lose more acid in the vomitus. The increased incidence in the babies with trachea-oesophageal fistula may well reflect a kick-start to gastric acidity at birth due to the absence of alkaline amniotic fluid in the stomach [5]. PS babies with alkalosis can be rendered more quickly fit for surgery with H2 receptor blockers (cimetidine) than by waiting for the perfused neonatal kidneys to restore the acid-base status [33].

The Male Preponderance

The only accessible comparative study of acid secretion between the sexes involved 43 premature but otherwise normal infants. Free and total acidity was measured in each baby on 10 consecutive days after birth. The total average acidity for boys was 61.1 units compared to 35.2 units for girls in the second period of 5 days [34]. Such a study is unlikely to be repeated.

We should not be surprised at this. Adult males have a greater parietal cell mass and greater acidity than females. The incidence of duodenal ulcer (DU) among adult males is 5 times greater than in females- the same sex-ratio displayed in PS. Both PS babies and adults with DU also share the same preponderance of blood group O-especially with a non-secretor status [35,36]. In these respects PS is the baby form of DU.

The onset at 4 weeks and not at birth

Peak acid levels are reached at around 2 - 3 weeks of age. The acid induced work-hypertrophy of the sphincter is aided by the trophic effects of the high gastrin levels at that time. Hence the condition is classically acquired several weeks after birth.

Self-cure with time

When the negative feedback develops, acidity falls and the lumen widens with age. The trophic effect of gastrin reduces when gastrin levels fall. It is also possible that, with time, the baby maybe more selective and will not allow overfeeding when his stomach is already filled. The acid producing effect of a narrowed gastric outlet observed in both adults with PS and rats subjected to artificial narrowing of the pylorus will also be lost [26,27].

Family History and First-Born status

25% of PS babies will have a family history and the concordance rate in monozygotic twins varies from 0.25 - 0.44 [13]. What is inherited is the tendency to have a parietal cell mass at the upper end of normal. The first-born baby will have a first-born mother-more likely to continue to offer feeds to her vomiting son. Feeds provoke the most intense and frequent pyloric contractions (Figure 2).
Dr. John Thomson’s mild cases/Erythromycin and Underfeeding

The presence of mild cases being “not at all uncommon” – cured by dietary restriction, should come as no surprise. Basically at some point in the hyperacidity pathogenesis active food related work hypertrophy will compete with time related falling acidity. Undernutrition (and other supportive measures) may lead to temporary improvement or cure. Inappropriate overfeeding may lead to further outlet obstruction. The baby may slip in and out of clinical PS. It is dynamic and not uncommon.

Erythromycin is a motilin agonist. Motilin induces gastric peristalsis with its consequent effect on further pyloric contraction [3].

Cautious underfeeding remains in theory and in practice an essential step in achieving a medical or spontaneous cure [37].

In 1976 Prof. John Dodge investigated the possibility that maternal stress facilitated PS. He used pentagastrin (PG) as a proxy for stress and injected it into 20 pregnant dogs before labour. 28% of the 84 pups developed PS indistinguishable from the human variety. 16% developed superficial duodenal ulcers. When PG injections were also given to the pups even more developed PS [34]. The implications were obvious:

1. PG was transferred to the babies in utero and caused hyperacidity in the pups.
2. Hyperacidity causes PS.

It has since been established that maternal gastrin itself is transferred in the dog from to the foetus and causes gastric acid secretion [39]. In sheep, foetal gastrin secretion begins 2 weeks before birth and continues thereafter [40].

What are we to make of these observations? Acid in the neonatal stomach is known to reduce early enteric infections. Normal transplacental gastrin transfer starts the process and an impaired negative feed-back continues the process.

The positive result is fewer enteric infections and the negative result is PS in babies who inherit an acid secreting ability at the upper end of normal.

In the last 10 - 20 years there have been reports of a general decline in the incidence of PS in Europe and in Scotland [41,42]. A decline of greater than 30% has been recorded. During this time here has been a huge increase in the prescription of proton pump inhibitors (PPI) in neonatal practice generally to combat suspected gastro-oesophageal reflux (GORD). This association is unlikely to arise by chance [34].

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A fuller explanation of the hyperacidity theory is available in The Consequences and Cause of Pyloric Stenosis of Infancy Dr. Fred. Vanderbom MA and I.M.Rogers FRCS Obtainable from More Books (Lambert Academic Publishing).

Conflicts of Interest

There are no conflicts of interest.

Bibliography


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