Pyloric stenosis a 100 years after Ramstedt

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SUMMARY

Conrad Ramstedt performed the first pyloromyotomy for what is now called idiopathic hypertrophic pyloric stenosis 100 years ago. The intervening century has seen the management of this condition transformed but the underlying cause remains a mystery. This article reviews the treatment of this condition before and after the introduction of pyloromyotomy and the advances made subsequently towards understanding its cause.

INTRODUCTION

The clinical scenario is familiar and gratifying. An infant a few weeks old presents with vomiting of gradually increasing severity. Examination reveals mild dehydration and careful inspection identifies visible peristalsis. Opinions differ as to whether a pyloric mass is palpable. Investigation shows hypokalaemia and a raised bicarbonate. An ultrasound scan duly confirms a diagnosis of pyloric stenosis and after correction of any fluid and electrolyte imbalance pyloromyotomy is performed as a minor and trivial procedure. The infant disappears from the ward and you meet by chance a few weeks later. A happy infant with an invisible abdominal scar beams at you from the lap of a delighted parent.

How different from a 100 years ago when most infants with this condition died in an emaciated state after months of misery (figure 1). Just 30 years after Ramstedt introduced pyloromyotomy, Mack could write with justification in 1942 that 'Present day methods of diagnosis and treatment of hypertrophic pyloric stenosis of infants may well be classed among modern medical miracles'.[1]

Yet despite this triumphant advance, the exact cause of what is now designated idiopathic hypertrophic pyloric stenosis (IHPS) remains a mystery. In this short review, we consider the early history of recognition of this condition, how management evolved in the last century and what advances in our understanding of IHPS have taken place. Lastly, we ask whether further advances could one day relegate Ramstedt's pyloromyotomy to the history books.

EARLY DESCRIPTIONS

Hirschsprung is credited with the first unequivocal modern description of IHPS in 1888.[2] There are at least seven earlier case reports published in the preceding 300 years including those of Blair (1717), Armstrong (1777) and Beardsley (1788), the latter report being discovered and reported by Sir William Osler.[1]

Hirschsprung reported two cases. The first, a girl, was born at term and began violent vomiting

Figure 1 Infant with pyloric stenosis (reproduced from Rankin W. Lessons on the Surgical Diseases of Childhood. Alex Macdougall, Glasgow 1933).

at age 10 days. She lost weight and died at age 30 days weighing less than at birth. Autopsy revealed a firm, cylindrical thickening of the pyloric canal consisting of hypertrophy of all layers, particularly the muscularis. The second case, also a girl born at term, was complicated by the coexistence of miliary tuberculosis. Vomiting began by 14 days and she died at age 6 months. At autopsy, there were miliary tubercles in various organs, the stomach was dilated, the pyloric canal was elongated to 3 cm and its wall was hypertrophied, particularly the muscle layer. Case reports multiplied rapidly after this and by 1910 there were 598 published cases.

Epidemiology

IHPS has attracted much attention from epidemiologists and MacMahon provides a very useful recent review of the literature.[3] Certain observations appear consistent. It has occurred in the Western world throughout the last century with an incidence of between 2 and 5 per 1000 live births but is less common elsewhere. The latter may of course reflect under ascertainment but it is clearly less common in black and Asian ethnic groups in the USA where such bias is excluded.

A fourfold to fivefold higher risk of the disease in boys than girls appears in all studies. Still was the

first to record (in 1927) that it was more common in first-born children.[4] However, MacMahon's analysis of a series of cases providing information on birth order suggested a general decline in risk with increasing birth order rather than a unique position for first born.

Epidemiological studies have provided several important clues to aetiology as described below. Recurrence risk in families and twin studies provide unequivocal evidence of a genetic contribution and maternal smoking and postnatal erythromycin administration have been suggested as environmental factors. Sharp declines in the incidence of IHPS in Denmark and Sweden during the 1990s, coincident with successful campaigns to discourage the prone sleeping position, led to the hypothesis that sleeping prone may be a risk factor.

It is amusing to note in retrospect that IHPS was regarded as a disease of children of the intellectual classes. In fact, early progress in the study of IHPS depended to an unusual degree on infant offspring of physicians with the disease: Dent's successful pyloroplasty (1902) and Ramstedt's pyloromyotomy (1912) were both performed on children of physicians.

Aetiology

It is well established that IHPS arises from a genetic predisposition interacting with environmental factors. As yet, however, no causal gene or sequence variant has been identified and the pathophysiology at a molecular level remains unknown.

Genetics

Armstrong (1777) was the first to report familial occurrence of pyloric stenosis, but clear evidence for a genetic predisposition required more affected individuals to survive to reproductive age. Carter's classic studies established non-syndromic pyloric stenosis as a complex, multifactorial, sex-modified threshold trait.[5 6] A later re-analysis of data from several studies concluded that IHPS is determined by two or three loci of moderate effect conferring individual genotype relative risks of up to 5.[7]

IHPS has also been associated with several genetic syndromes, such as Cornelia de Lange and Smith-Lemli-Opitz syndromes, and chromosomal abnormalities, including translocation of chromosome 8 and 17 and partial trisomy of chromosome 9. Autosomal-dominant monogenic forms of IHPS have also been reported in several extended pedigrees.

A recent population-based cohort study of 2 million children born in Denmark between 1977 and 2008 has provided further evidence that familial aggregation among the 3362 infants with IHPS is mostly due to shared genes rather than maternal factors operating during in utero development or a common family environment.[8] Segregation was not mendelian but the data did not allow a particular model of inheritance to be determined.

Linkage and association studies

Five genetic loci have been identified, IHPS1–5, by linkage analyses. IHPS1 is NOS1 which encodes the enzyme neuronal nitric oxide synthase and was evaluated as a functional candidate on account of evidence that a defect in nitric oxide production may have a role in the aetiology of IHPS, as discussed below. However, the evidence for linkage and association is weak and has not been replicated. Two loci, IHPS2 (16p13–p12) and IHPS5 (16q24.3) have been identified in pedigrees displaying autosomal dominant inheritance.[9 10] Locus heterogeneity is therefore established for the monogenic form but the corresponding genes have yet to

be identified. A genome-wide single nucleotide polymorphism (SNP)-based high-density linkage scan carried out on 81 small nuclear pedigrees identified IHPS3 on chromosome 11q14–q22 and IHPS4 on Xq23.[11] The two linked chromosomal regions each harbour functional candidate genes that are members of the canonical transient receptor potential (TRPC) family of ion channels and have a potential role in smooth-muscle control and hypertrophy: TRPC6 and TRPC5. Further analysis provided suggestive evidence for a third locus on chromosome 3q12–q25, a region which harbours a third TRPC gene, TRPC1.[12] Fine mapping of all three genes using a tagSNP approach and re-sequencing identified a SNP in the promoter region of TRPC6 and a missense variant in exon 4 of TRPC6, which may be putative causal variants.

Environmental factors

Recent evidence suggested two factors for which plausible biological explanations exist: infant sleeping position and postnatal erythromycin exposure.

A recent striking decline in the incidence of IHPS in Denmark and Sweden appears to have coincided with an increase in numbers of infants placed in the supine rather than prone sleeping position after the realisation that prone sleeping was a risk factor for sudden unexplained death in infancy and the consequent 'back to sleep' public health interventions.[13 14] However, although a recent study of the incidence of IHPS and sudden infant death syndrome (SIDS) in Scotland in the period 1981–2004 showed a similar decline and linear correlation between rates for the two conditions, the decline in IHPS rates preceded that for SIDS by 2 years.[15] The observation that the prone position is associated with pooling of milk in the gastric antrum rather than the fundus could provide a biological basis for the effect of sleeping position if such pooling exacerbated pyloric smooth muscle contraction.

Several studies have reported a small increase in risk of IHPS in infants exposed to erythromycin in the postnatal period, although maternal ingestion either prenatally or during breast feeding does not seem to alter risk.[16 17] Erythromycin has gastrokinetic effects mediated by its action as a motilin receptor agonist which could lead to abnormal or excessive pyloric/gastric motility.

Pathophysiology

Measurements of blood hormone levels and detailed examination of pyloric biopsy material has been undertaken. The latter is of course 'end-stage' tissue and the distinction between primary and secondary changes is difficult to make. Abnormalities have been observed in gastrin levels, enteric nerve terminals, nerve supporting cells, interstitial cells of Cajal, smooth muscle cells, growth factor synthesis and receptors, and extracellular matrix.[18] The control and regulation of pyloric sphincter function is a complex system involving the intrinsic myogenic activity of smooth muscle, the pacemaker cells of the interstitial cells of Cajal, gut hormones, and the autonomic and enteric nervous systems, and it seems likely that defects in many different aspects of this system could cause IHPS.

The hypothesis that in a subset of cases a primary defect in production of nitric oxide by nitrergic nerves of the enteric nervous system leads to failure of relaxation of pyloric smooth muscle has support from several lines of evidence.[19 20]

Clinical management

Treatment pre Ramstedt: medical and surgical

Before Ramstedt, attempts at treating IHPS were developed from two opposing concepts: the 'spasm first' theory supported primary pyloric spasm and secondary hypertrophy while the 'hypertrophy first' belief advocated the reverse. Medical approaches were largely adopted by believers in the 'spasm first' theory of IHPS whereas proponents of surgery adhered to hypertrophy as the primary problem.

Medical treatment

Medical treatments aimed mainly at releasing the pyloric spasm included the use of gastric lavage, several antispasmodic drugs and dietary measures. Gastric lavage, frequently with a bicarbonate solution, was employed in the belief that the pyloric spasm was the result of excess gastric acid. Numerous antispasmodic drugs tried included belladonna, opium, cocaine and atropine to inhibit vagal activity. Dietary measures encompassed iced milk, frequent small feeds and the use of thickened feeds or 'gruel' made by mixing milk and flour. In addition, attempts were made to maintain nutrition and hydration by nutrient milk enemas and saline administered rectally or subcutaneously.

Surgical treatment

The first surgical attempts, undertaken near the end of the nineteenth century, were designed either to bypass the obstruction or relieve it by a direct attack on the pylorus.[21 22] The first successful operation was gastro-enterostomy performed by Lobker in 1898. The infant was 10 weeks old and made a full recovery. Up to 1900, seven gastro-enterostomies were performed with three deaths.

The first attempt to relieve obstruction, by James Nicholl of Glasgow in 1899, was by divulsion of the pylorus (Loreta's operation) using a mechanical dilator introduced through the stomach. However, it seems that he doubted the efficacy of this operation as he advocated combining it with gastro-enterostomy. By 1904, he had done nine of these operations with three deaths.

In 1902, Clinton Dent, working with Edmund Cautley at the Belgrave Hospital for Children, introduced complete pyloroplasty, using the Heineke-Mikulicz technique in which a longitudinal incision extending through all the layers of the pylorus, including the mucosa, was converted into a transverse one. Dent had a 75% success but others were less successful. Eventually the operation was abandoned because of the frequency of peritonitis and technical difficulties such as suturing the cut edges of the hypertrophic pylorus.

In 1906, James Nicoll introduced the extramucous method of partial pyloroplasty. He reported six cases with one death. However, he advised combining it with the Loreta dilatation and for this reason his operation did not receive recognition as the forerunner of Ramstedt's pyloromyotomy.

In 1907, Fredet of Paris performed the first extramucous pyloroplasty on a 10-week-old infant with pyloric stenosis and the infant survived. However, he still recommended combining the operation with gastroenterostomy. Weber (in 1910) independently performed the same procedure of extramucous or submucous partial pyloroplasty.

The situation pre Ramstedt was well summarised in a meeting of the Clinical Society of London in 1907.[23] Dr G F Still reported on 23 cases of which 14 had survived and 9 had died, with near equal numbers in each group treated medically or surgically. Dr Voelcker analysed 39 cases managed at Great Ormond Street Hospital. Thirty-four had died of whom only five had been operated on. Comparing the dire Great Ormond Street Hospital data with surgical treatment, a series published in 1907 reported mortalities for gastroenterostomy 53%, for pyloroplasty 49%, for divulsion 39% and for extramucous pyloroplasty 17%. The question remained, as Dr Voelcker remarked: 'Should the child be saved by surgery or from surgery?'

Ramstedt and pyloromyotomy

On 23 August 1911, Ramstedt performed the first pyloromyotomy. We have an exact account of how he came to do it from a letter he wrote in 1957 at the age of 80, quoted by Selwyn Taylor.[24] He had been invited to treat congenital pyloric stenosis in the first-born son of a noble family in the district; this was the first case of the condition he had seen. He decided to perform extra-mucosal pyloroplasty and described what happened at the operation:

> At the laparotomy on 23 August 1911, I was astonished at the pyloric tumour as thick as my thumb. After I had split the tumour down to the mucosa for a distance of about 2 cm, I had the impression that the stenosis had been relieved. I still tried to accomplish the plastic procedure by transverse suture of the muscle edges. However the tension on the sutures was so strong that the first one cut through immediately. Then the thought shot through my head: 'A plastic alteration of the cut edges is completely unnecessary; the stenosis seems to be already relieved by a simple splitting of the pyloric muscle and coincidentally the spasm as well, which is the characteristic basis of the disease'. I did not complete the plastic operation on the muscle which had been planned, but left the cut gaping, covering it with a tab of omentum for safety's sake and ended the operation. The little one vomited a few times for the first few days which I attributed to the sutures placed at the beginning, but he recovered promptly and completely to the great joy of his parents.

He performed the operation on a second case on 18 June 1912 and reported both to the Natural Science Assembly in Munster in September of that year.[25]

Conrad Ramstedt (1867–1963) was born in Prussia (figure 2). He served as a military surgeon in the First World War and was appointed chief surgeon to the Rafaelsklinik at Munster in 1919 where he spent his civilian working life. Eponym connoisseurs are aware that his name is spelled Rammstedt in the original publications but Ramstedt in publications after 1920. It appears that he discovered after the first war that Rammstedt with two 'm's was an error introduced by his grandfather into the church records so reverted to the original spelling. A case can therefore be made for either spelling.

Pyloromyotomy: the first 100 years

Pyloromyotomy was adopted quickly in the USA but adoption in the UK was delayed by the 1914–1918 war. The first Ramstedt operation in England was carried out at the Belgrave Hospital by Mr Robert Ramsay (at Dr Cautley's request) on 16 July 1918. The child died 1 week later although at postmortem the stenosis was shown to have been relieved. Ramsay went on to perform this operation over 200 times but initial results were disappointing. He published a paper in 1921 describing the outcome of the first 10 cases he treated with Ramstedt's pyloromyotomy: mortality was 50%. The poor state of nutrition and hydration of the infants and the relatively crude state of anaesthesia and perioperative care at that time obscured the true value of the procedure.
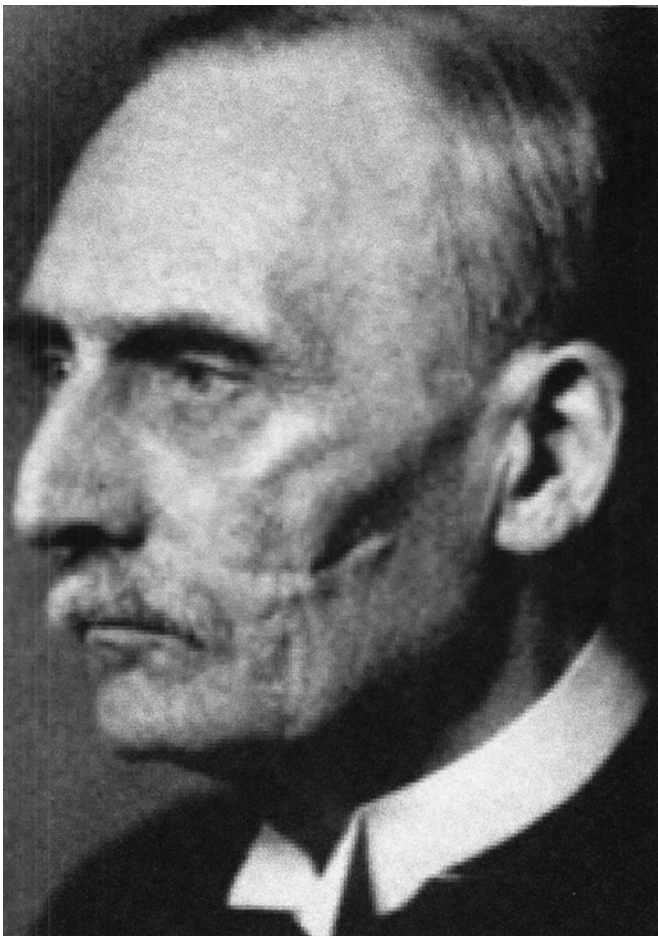
Figure 2 Conrad Ramstedt (reproduced from Taylor[23]).

By mid-century, however, the transformation had been such that Harald Mack could justly claim a modern medical miracle. In a series of 1422 cases operated on at Los Angeles Children's Hospital between 1934 and 1955 there were just 25 deaths (1.7%), many of which were from conditions unrelated to the IHPS or pyloromyotomy (eg, meningitis, multiple anomalies).[26]

The introduction of ultrasound imaging for diagnosis[27] was a significant advance and debate currently centres around the advantages and disadvantages of open versus laparoscopic pyloromyotomy.[28]

MODERN APPROACHES TO MEDICAL MANAGEMENT

Some cases of IHPS will resolve on medical treatment with antispasmodic drugs and recognition of this has prompted periodic enthusiasm for medical treatment, most recently in Asia.

Jacoby reported on 195 cases managed between 1944 and 1960 in which he used medical treatment with reduced feeds and atropine methylnitrate (eumydrin) successfully in about half of the cases, selected on strict criteria including later presentation.[29] As recently as 1991, Swift and Prossor questioned whether modern management should always be surgical, citing 7 of 62 cases treated successfully with eumydrin between 1979 and 1985 and noting the relatively high complication rate for surgery.[30]

Oral antispasmodics are problematic of course in a condition causing projectile vomiting, and an alternative strategy using intravenous atropine initially has been adopted in the recent past.[31] Prolonged hospitalisation is required (median 13 days) and oral atropine therapy has to be continued after discharge. Long-term outcome was good and pyloric muscle thickness normalises after this medical treatment, but the approach only seems justified in situations when expert paediatric surgery is not available.

CONCLUSIONS

In the 100 years since Ramstedt described his operation, the management of IHPS has been transformed beyond recognition. However, the underlying pathophysiology of the condition remains a mystery.[32] What will the next 100 years bring? It does not seem too optimistic to predict that advances in molecular genetic analysis, particularly new generation sequencing, will allow the molecular genetic basis and hence the molecular pathophysiology of IHPS to be determined. Heterogeneity at the molecular level can be anticipated, but it seems likely that the final common pathway will involve the control of pyloric smooth muscle contractility. If common causal sequence variants are identified it is perhaps not too fanciful to suggest that infants at risk might be identified at birth by DNA screening and manipulation of environmental factors such as feeding together with medication tailored to the molecular cause might render IHPS a preventable disease. The saga continues.

REFERENCES

1. **Mack HC.** A history of hypertrophic pyloric stenosis and its treatment. *Bull Hist Med* 1942;**12**:465–485.
2. **Hirschsprung H.** Falle von angeborener pylorus stenose, beobachtet bei sauglingen. *Jahrb der Kinderh* 1888;**28**:61–68.
3. **MacMahon B.** The continuing enigma of pyloric stenosis of infancy: a review. *Epidemiology* 2006;**17**:195–201.
4. **Still GF.** Place in family as a factor in disease. *Lancet* 1927;**2**:795–853.
5. **Carter CO.** The inheritance of congenital pyloric stenosis. *Br Med Bull* 1961;**17**:251–4.
6. **Carter CO**, Evans KA. Inheritance of congenital pyloric stenosis. *J Med Genet* 1969;**6**:233–54.
7. **Mitchell LE**, Risch N. The genetics of infantile hypertrophic pyloric stenosis. A reanalysis. *Am J Dis Child* 1993;**147**:1203–11.
8. **Krogh C**, Fischer TK, Skotte L, *et al*. Familial aggregation and heritability of pyloric stenosis. *JAMA* 2010;**303**:2393–9.
9. **Capon F**, Reece A, Ravindrarajah R, *et al*. Linkage of monogenic infantile hypertrophic pyloric stenosis to chromosome 16p12–p13 and evidence for genetic heterogeneity. *Am J Hum Genet* 2006;**79**:378–82.
10. **Everett KV**, Capon F, Georgoula C, *et al*. Linkage of monogenic infantile hypertrophic pyloric stenosis to chromosome 16q24. *Eur J Hum Genet* 2008;**16**:1151–4.
11. **Everett KV**, Chioza BA, Georgoula C, *et al*. Genome-wide high-density SNP-based linkage analysis of infantile hypertrophic pyloric stenosis identifies loci on chromosomes 11q14-q22 and Xq23. *Am J Hum Genet* 2008;**82**:756–62.
12. **Everett KV**, Chioza BA, Georgoula C, *et al*. Infantile hypertrophic pyloric stenosis: evaluation of three positional candidate genes, TRPC1, TRPC5 and TRPC6, by association analysis and re-sequencing. *Hum Genet* 2009;**126**:819–31.
13. **Nielsen JP**, Haahr P, Haahr J. Infantile hypertrophic pyloric stenosis. *Dan Med Bull* 2000;**47**:223–225.
14. **Persson S**, Ekbom A, Granath F, *et al*. Parallel incidences of sudden infant death syndrome and infantile hypertrophic pyloric stenosis: a common cause? *Pediatrics* 2001;**108**:E70.
15. **Sommerfield T**, Chalmers J, Youngson G, *et al*. The changing epidemiology of infantile hypertrophic pyloric stenosis in Scotland. *Arch Dis Child* 2008;**93**:1007–11.
16. **SanFillippo JA.** Infantile hypertrophic pyloric stenosis related to ingestion of erythromycin estolate. *J Pediatr Surg* 1976;**11**:177–180.
17. **Honein MA**, Paulozzi LJ, Himelright IM, *et al*. Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromcyin: a case review and cohort study. *Lancet* 1999;**354**:2101–5.

18. **Panteli C.** New insights into the pathogenesis of infantile pyloric stenosis. *Pediatr Surg Int* 2009;**25**:1043–52.
19. **Vanderwinden JM**, Mailleux P, Schiffmann SN, *et al*. Nitric oxide synthase activity in infantile hypertrophic pyloric stenosis. *N Engl J Med* 1992;**327**:511–5.
20. **Huang PL**, Dawson TM, Bredt DS, *et al*. Targeted disruption of the neuronal nitric oxide synthase gene. *Cell* 1993;**75**:1273–86.
21. **Mack HC.** A history of hypertrophic pyloric stenosis and its treatment. *Bull Hist Med* 1942;**12**:595–615.
22. **Mack HC.** A history of hypertrophic pyloric stenosis and its treatment. *Bull Hist Med* 1942;**12**:666–689.
23. **Sutherland GA.** Clinical Society of London meeting, Congenital Pyloric Stenosis, Mar 8 1907. *BMJ* 1907;**1**:627–628.
24. **Taylor S.** Pyloric stenosis before and after Ramstedt. *Arch Dis Child* 1959;**34**:20–3.
25. **Rammstedt C.** Zur operation der angeborenen Pylorus Stenose. *Med Klin* 1912;**8**:1702–1705.
26. **Pollock WF**, Norris WJ, Gordon HE. The management of hypertrophic pyloric stenosis at the Los Angeles Childrens Hospital: a review of 1,422 cases. *Am J Surg* 1957;**94**:335–48.
27. **Teele RL**, Smith EH. Ultrasound in the diagnosis of idiopathic hypertrophic pyloric stenosis. *N Engl J Med* 1977;**296**:1149–50.
28. **Hall NJ**, Pacilli M, Eaton S, *et al*. Recovery after open versus laparoscopic pyloromyotomy for pyloric stenosis: a double-blind multicentre randomised controlled trial. *Lancet* 2009;**373**:390–8.
29. **Jacoby NM.** Pyloric stenosis: selective medical and surgical treatment. A survey of sixteen years' experience. *Lancet* 1962;**1**:119–21.
30. **Swift PG**, Prossor JE. Modern management of pyloric stenosis—must it always be surgical? *Arch Dis Child* 1991;**66**:667.
31. **Kawahara H**, Takama Y, Yoshida H, *et al*. Medical treatment of infantile hypertrophic pyloric stenosis: should we always slice the 'olive'? *J Pediatr Surg* 2005;**40**:1848–51.
32. **Chung E.** Infantile hypertrophic pyloric stenosis: genes and environment. *Arch Dis Child* 2008;**93**:1003–4.