

Increased serum immunoreactive gastrin levels in idiopathic hypertrophic pyloric stenosis¹

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SUMMARY The serum immunoreactive gastrin (IRG) level in infants with confirmed idiopathic hypertrophic pyloric stenosis (IHPS) has been determined and compared to that found in vomiting infants without IHPS, in normal infants, and in normal adults. The mean serum IRG level of normal infants (103 ± 9 pg/ml (mean \pm SEM) exceeded that of normal adults (28 ± 5 pg/ml). The pre-operative mean serum IRG level in IHPS infants (256 ± 26 pg/ml) was significantly higher than that of both normal infants and vomiting infants without IHPS (93 ± 9 pg/ml). Twenty-five per cent (5/20) of the IHPS infants had serum IRG levels within the upper range of normal infants. Fasting serum IRG levels in IHPS infants were not altered immediately by pyloromyotomy. The results from this study suggest a relationship between gastrin and idiopathic hypertrophic pyloric stenosis.

Although the pathological and anatomical changes accompanying idiopathic hypertrophic pyloric stenosis (IHPS) are well documented, the aetiology and pathogenesis of this condition are unknown. Several studies (Dodge, 1970; Karim *et al.*, 1974; Dodge and Karim, 1976) have demonstrated that when pentagastrin injections were administered to pregnant bitches their offspring developed hypertrophic pyloric stenosis; this finding prompted a hypothesis that gastrin is an aetiological factor in human IHPS (Dodge, 1972; Dodge and Karim, 1976). At present, the status of the gastrin hypothesis in human IHPS is uncertain because evidence has been presented both to support (Spitz and Zail, 1976) and refute (Rogers *et al.*, 1975) it. No systematic evaluation of fasting and postprandial serum IRG levels in infants has been undertaken to establish the normal fasting and stimulated ranges of IRG. Available evidence indicates that a neonatal hypergastrinaemia does exist (Rogers *et al.*, 1974; Sann *et al.*, 1975; Euler *et al.*, 1977).

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A number of different serum IRG components with varying molecular size have been found in adults (cf. Walsh, 1977). It is claimed that 45% of neonatal serum IRG is 'big-big' gastrin (Torsoli *et al.*, 1975).

The present study examines serum immunoreactive gastrin (IRG) levels pre- and postoperatively in a group of infants with confirmed IHPS. These values have been compared to those found in vomiting infants without IHPS, in normal infants, and in normal adults. In addition, the distribution of serum IRG components has been studied by Sephadex G-50 gel chromatography in preoperative IHPS and normal infants' samples.

Methods

SUBJECTS

Fasting venous blood samples were obtained from 20 infants with IHPS preoperatively, from five vomiting infants without IHPS, from 18 normal infants hospitalised for elective procedures—for example, hernia repair, circumcision, congenital dislocated hip repair—and from 20 normal adults. The diagnosis of idiopathic hypertrophic pyloric stenosis (IHPS) was made on clinical history and by palpation of the pyloric mass; this diagnosis was confirmed at operation in all 20 infants. Oral gastric aspiration of the stomach was performed in the operating room before the induction of anaesthesia. Less than 25 ml of

mucoid gastric contents (pH 6.0) were aspirated from each infant's stomach. Five other infants with projectile vomiting but no palpable pyloric mass underwent barium study to confirm the absence of pyloric stenosis.

BLOOD SAMPLING

Blood samples were obtained from all IHPS and vomiting infants after at least a 12 hour fast. None of the infants had received any preoperative medication before the blood sampling. Intravenous infusions were running during this period; the nature and volume of solution selected for infusion were based upon the severity of the electrolyte abnormality and clinical status of hydration in each particular infant. Infants received the following solutions: 5% dextrose together with normal saline, one-half strength saline or one-quarter strength saline; each solution was supplemented with 5 mmol KCl/250 ml. No attempt was made at nasogastric decompression. All infants studied with barium had blood samples obtained before the barium study. Sixteen to 80 hours after pyloromyotomy, when at least three formula (Enfalac) feedings had been tolerated without vomiting, a fasting blood sample was taken from seven of the IHPS infants. The blood was drawn just before the next scheduled feeding four hours later as this constituted the longest fasting period in infants of this age. Normal infants' blood was taken also four hours after formula (Enfalac) feeding with or without cereal (Pablum). Blood from normal adults was obtained after an overnight fast. From all test groups venous blood was collected, allowed to clot, centrifuged, and the serum stored at -20°C . Serum immunoreactive gastrin (IRG) level was determined in duplicate by a gastrin radioimmunoassay described elsewhere in detail (Mayer *et al.*, 1974).

GEL CHROMATOGRAPHY

Three sera from preoperative IHPS infants and three from normal infants were chromatographed upon a Sephadex G-50F column (1.0×200.0 cm) in $0.2 \text{ M NH}_4\text{HCO}_3$. The column was calibrated with natural, human G-34 and G-17; the gastrin components were gifts from Professor R. A. Gregory, Liverpool. Serum volumes applied ranged from $0.5\text{--}1.2$ ml. One millilitre consecutive fractions were collected commencing just before the void volume (40 ml) and finishing at the excluded volume (140 ml). All column fractions were lyophilised and odd-numbered tubes assayed with antibody for IRG content and even-numbered tubes assayed without antibody for the unspecific binding. The average IRG recovery from the column was 88%.

Statistical evaluation of the data was performed by Student's *t* test. This project was approved by the

Scientific and Ethics Committee of The Hospital for Sick Children, Toronto, and written consent was obtained from parents of all test subjects.

Results

The numbers, sex distribution, and age of the groups studied are listed in Table 1. Since no differences existed between male and female serum IRG values, all values in each group were pooled for the calculations. The mean fasting serum IRG values for the normal adults, normal infants, preoperative IHPS infants, and vomiting infants without IHPS are shown in Fig. 1. Normal infants showed a significant rise of serum IRG above the adult value ($P < 0.001$); the preoperative IHPS infants showed a further significant increase above both the normal infant ($P < 0.001$) and adult values ($P < 0.001$). The serum IRG in vomiting infants without IHPS, although above the adult values, was significantly lower than the preoperative IHPS infants ($P < 0.001$).

Table 1 Number, sex distribution, and age of study groups

Group	Number	Sex		Age (days)
		Male	Female	
Normal infants	18	14	4	2-98
IHPS* infants				
Preoperative	20	15	5	17-95
Postoperative	7	4	3	22-70
Vomiting infants	5	5	0	9-60
Normal adults	20	14	6	18-37 yr

*Idiopathic hypertrophic pyloric stenosis.

The age distribution of serum IRG levels in IHPS and normal infants is illustrated in Fig. 2. Normal infants' levels ranged from 25-162 pg/ml; IHPS infants' from 115-623 pg/ml. Five of the IHPS infants' levels were within the upper range of normal infants. IHPS infants' pre and postoperative fasting serum IRG levels were not significantly different (Table 2).

Sephadex G-50 gel chromatography of three preoperative IHPS and three normal infants' sera revealed one major IRG peak having an IRG elution profile comparable to G-34. A representative Sephadex G-50 elution profile is presented in Fig. 3. No significant IRG activity was detected in the void volume of the column, the elution position of 'big-big' gastrin. The unspecific binding was comparable across the column fractions and not different from the unspecific binding of the gastrin radioimmunoassay.

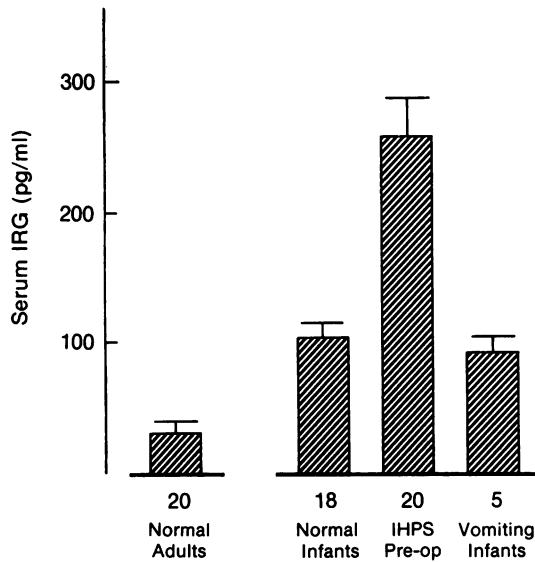


Fig. 1 Comparison of mean (\pm SEM) fasting immunoreactive gastrin (IRG) levels found in normal adults, in normal infants, in infants with idiopathic hypertrophic pyloric stenosis preoperatively (IHPS Pre-op), and in infants who vomit without IHPS (vomiting infants).

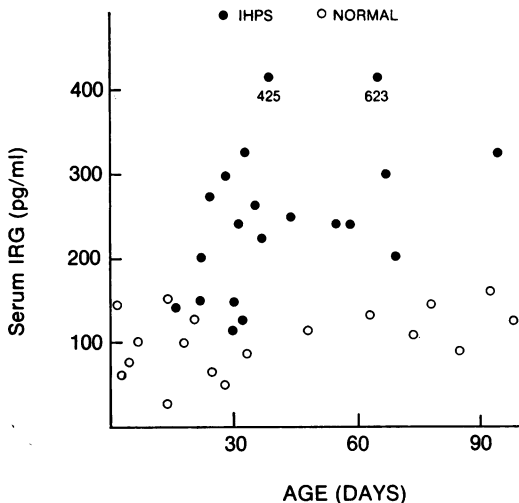


Fig. 2 Age distribution of serum immunoreactive gastrin (IRG) levels in preoperative infants with idiopathic hypertrophic pyloric stenosis and in normal infants.

Discussion

The results of this study confirm the presence of neonatal hypergastrinaemia (Rogers *et al.*, 1974; Sann *et*

Table 2 IHPS* infants: Pre and postoperative mean fasting serum immunoreactive gastrin (IRG) levels

	Number	IRG (pg/ml) ($m \pm$ SEM)
Preoperative	20	256 \pm 26
Postoperative	7	228 \pm 30

*Idiopathic hypertrophic pyloric stenosis.

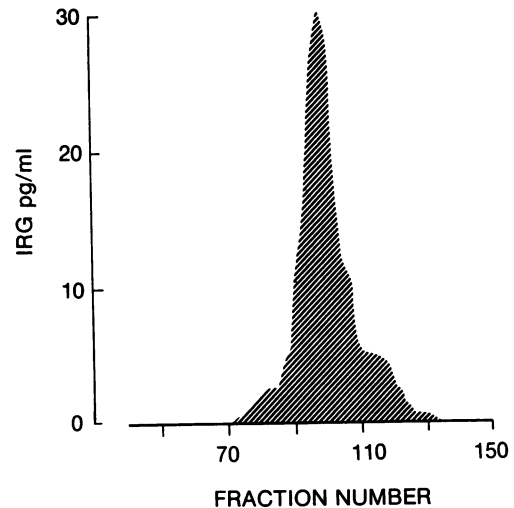


Fig. 3 A representative Sephadex G-50 immunoreactive gastrin (IRG) elution profile of a preoperative IHPS infant's serum. Major IRG peak corresponds to the elution position of G-34.

al., 1975; Euler *et al.*, 1977) and provide evidence for an even greater rise in most infants with idiopathic hypertrophic pyloric stenosis (IHPS). The raised serum IRG is not due to age differences between the IHPS and normal infants because both groups have comparable age distributions and within this range no effect of age upon the IRG levels was observed (Fig. 2). Furthermore, the immediate preoperative aspiration of mucoid gastric contents eliminates the possibility of residual food in the stomach causing the raised serum IRG in the IHPS infants. Pyloromyotomy has no immediate effect upon fasting serum IRG levels indicating that the pyloric stenosis is not the cause of the raised serum IRG.

The Sephadex G-50 IRG elution profiles reveal that G-34 is the major circulating IRG component in the neonatal sera examined. No evidence was found to support the claim of 45% 'big-big' gastrin in neonatal sera (Torsoli *et al.*, 1975).

A controversy exists as to whether or not serum IRG is raised in IHPS infants (normal—Rogers *et al.*, 1975; raised—Spitz and Zail, 1976). From a

consideration of the available data this discrepancy can be resolved. First, how long was the preoperative fasting period before the blood sample was drawn and how were the infants treated during this time? In the present study, blood samples were drawn from IHPS infants after at least a 12 hour fast during which time the infants were on intravenous fluids; normal infants' blood was drawn after a four hour fast. In the other studies, blood sampling was performed on the IHPS infants 'three hours after their last feed' (Rogers *et al.*, 1975) and 'immediately pre-operatively after a six hour fast' (Spitz and Zail, 1976). In these two reports, nothing is mentioned about the infants' preoperative clinical care.

The second and probably most important consideration is the comparison of *mean* serum IRG levels from normal and IHPS infants. These data are informative but also are misleading! In the present study, there is a significant ($p < 0.001$) rise of serum IRG in the IHPS infants (256 ± 26 pg/ml) compared to the normal infants (103 ± 9 pg/ml); however, 25% (5/20) of the IHPS infants have serum IRG levels within the upper range of the normal infants (Fig. 2). In another published series, 50% (9/18) of the IHPS infants have serum IRG levels within the upper range of the normal infants (Spitz and Zail, 1976). This overlap of serum IRG levels between IHPS and normal infants is probably the major reason for the current controversy about serum IRG levels in IHPS.

A recent report in which gastrin is shown to have a direct effect upon pyloric smooth muscle contraction (Rogers *et al.*, 1976) supports the gastrin hypothesis in IHPS. Results from the present study, revealing higher serum gastrin levels in most IHPS infants compared to normal infants, further support a role for gastrin in human IHPS.

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