Gastrointestinal motility disorders in children: etiology and associated behaviors

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Seasonal variations in the incidence of infantile hypertrophic pyloric stenosis in two Dutch regions

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Abstract

Objective
Seasonal variations in the incidence of infantile hypertrophic pyloric stenosis (IHPS) have been reported, but results have been contradictory and local factors have generally not been taken into account. The aim of this study was to investigate seasonal variations in IHPS incidence in two closely located but separate regions of a small country.

Study design
We studied IHPS children born between 1995 and 2009 in two regions of the Netherlands using hospital databases and a birth defect registry. Yearly, seasonal and monthly variations in IHPS incidence by date of birth were assessed by Chi square analyses and Walter and Elwood’s test for seasonality while correcting for the total number of live births. Correlation analyses were performed for local climate factors.

Results
In North-Holland, 612/475,941 (1.29/1,000) children developed IHPS, compared to 355/287,207 (1.24/1,000) in the Northern Netherlands. In North-Holland only, significant seasonal variation was found with a peak incidence in children born in December (p = .005). Only a weak correlation was found between incidence rates and climate factors for this region, and no significant correlation was found for the Northern Netherlands. There was no change in IHPS incidence over time during the study period.

Conclusions
We found a significant difference in IHPS incidence within the various parts of the year in one region, correlating weakly with local climate factors, and found significant differences between two closely located populations. Season specific environmental influences other than climate are likely to be involved in the pathophysiology of IHPS.
Introduction

Infantile hypertrophic pyloric stenosis (IHPS) is a common condition in infants characterized by an acquired narrowing of the pylorus. A progressive hypertrophy of the pyloric muscle results in a near-complete obstruction of the pylorus, causing the classical symptom forceful projectile postprandial vomiting. IHPS typically occurs between the third and sixth week of life in a formerly healthy infant. The incidence of IHPS varies between 1.5-2 per thousand live births in the Western World and has a striking male predominance (male : female ratio 4-5:1). Despite its relatively high incidence, the etiology of isolated IHPS is still poorly understood. The cause is suggested to be multifactorial, with an important role for genetic factors. Environmental factors, such as medication use, maternal age, maternal smoking and maternal drinking and feeding habits have been studied but the exact significance of most of these factors for developing IHPS remains unknown.

Several studies have reported seasonal variation in the incidence of IHPS, suggesting that extrinsic factors anywhere from conception to early postnatal life influence the anatomy of the pyloric muscle. Results of seasonal IHPS studies have been contradictory however, and some papers reported no seasonal variation in IHPS incidence. Complicating factors in comparing and interpreting results are the differences in definitions of seasons and differences in moments of measurement of incidences. Moreover, data come from various countries with important differences in climate and, thus, in seasonal characteristics, but also in genetic make-up, nutrition and cultural habits, complicating identification of shared associated influences.

We reasoned that further insight in possible seasonal influences in IHPS might be obtained by studying IHPS incidences in two different regions in a single country, as these regions will share many possibly confounding factors and causes of differences (if present) might be more easily determined. Therefore, we studied the incidence of IHPS in two regions of the Netherlands over a period of 15 years, with detailed attention to various local climate factors.

Methods

Study population

The Netherlands is a small, densely populated country (16,800,000 inhabitants; 404 inhabitants/km²). We studied children born in the province of North-Holland and the provinces Groningen, Friesland, Drenthe (Northern Netherlands) between 01.01.1995 and 31.12.2009 (Fig I).

The province of North-Holland in the Northwestern part of the Netherlands is a densely populated province (2,600,000 inhabitants; 980 inhabitants/km²) with a high rate of
immigrants (mean immigration rate of 9.8/1,000 inhabitants between 1995 and 2009). Pediatric surgical care is centered exclusively in the two academic centers in the province (both in Amsterdam) in which care is provided by a joint, single team of pediatric surgeons, and the larger regional center (in Alkmaar). Patients presenting with IHPS at smaller regional hospitals are referred to any of these three hospitals. The Northern Netherlands consists of the three most northern located provinces of the country, and is the most rural area of the country with a low population density (1,700,00 inhabitants; 205 inhabitants/km²) and a relatively low rate of immigrants (mean immigration rate of 5.9/1,000 inhabitants between 1995 and 2009). Pediatric surgical care is provided in the single academic hospital of the Northern Netherlands but IHPS is also surgically corrected in various regional hospitals.

We defined IHPS as an acquired hypertrophy of the pyloric muscle in infants occurring before 12 months of age and requiring pyloromyotomy. Newborns in whom pyloric stenosis was diagnosed prenatally or present at birth were excluded because of a presumed different cause. Redo pyloromyotomies were excluded. The control group consisted of all live births without IHPS in the two regions within the study period.

Data sources

In North-Holland the hospital surgical databases of the two academic hospitals and of the single large regional hospital were systematically searched for patients born within the study period who underwent a pyloromyotomy for IHPS (either by laparoscopy or laparotomy). Detailed patient characteristics were obtained from the hospital information systems using a standardized form.

Eurocat Northern Netherlands is a population-based birth defect registry covering the three Northern provinces since 1981. Children and fetuses with anomalies diagnosed before or after birth are eligible for registration at the Eurocat Northern Netherlands registry, if the mother lived in the region at the time of birth and the child has not reached the age of 16 at notification. There is no lower limit for gestational age, spontaneous and induced
abortions are included. Notification of children and fetuses with congenital anomalies is voluntary. Registry personnel are actively involved in case ascertainment, using multiple sources such as obstetric records, hospital administration data, and pathology records. Parental informed consent is needed for registration. IHPS cases registered in one study region can not be registered as a case in the other region, and the regions are geographically separated by a large lake (Figure I). Information on the number of live births in the two regions within the various parts of the study period was obtained from Statistics Netherlands. Daily climatologic data throughout the whole study period were obtained from the regional weather observation stations (station numbers 240, 270, 278 and 280) of the Royal Netherlands Meteorological Institute.

Data analysis
Baseline characteristics of the two regions were described as percentages and means with standard deviations or medians with interquartile ranges. Prematurity was defined as a gestational age of less than 37 weeks. Ethnic origin was not registered in either region, remained unavailable for the Northern Netherlands and could only be assessed based on surname and given name of the infants. The incidence of IHPS per 1,000 live births was based on date of birth and was calculated by dividing the number of IHPS cases by the total number of live births within a region born within a certain year, half year, season or month, respectively. Mean overall incidence rates were calculated for each region and were reported with standard errors of the mean and 95% confidence intervals. The definition of seasons was based on a climate categorization of month of birth: winter (December, January and February), spring (March, April and May), summer (June, July and August) and autumn (September, October and November). Comparisons between and within the regions were performed by using independent t-tests for normally distributed continuous data and Mann-Whitney U tests for skewed continuous data. Chi square tests were applied for comparisons of proportions. The Walter and Elwood’s test for seasonality was performed to test for specific seasonal variations in IHPS incidence by month of birth within the two regions, adjusting for variation in the number of live births at risk. This seasonality test allows it to estimate a time at which a maximum (direction of maximum: θ max) occurs in a postulated simple harmonic fluctuation during a certain period while correcting for variations in the population at risk. To assess internal consistency of data, baseline characteristics and variations in incidence of IHPS were compared between patients recruited from the two different academic centers in North-Holland (n=332 and n=216, respectively). This was not done for the single regional hospital in North-Holland as numbers were too small. For the Northern-Netherlands, no data were available to test for internal consistency in a similar way.
Mean monthly values for four different climate indices were calculated from daily values of the regional weather observation stations. In the Northern Netherlands, the mean values of the three regional weather observation stations (station numbers 270, 280 and 289) were calculated into a mean value of the region. Climate indices comprised air pressure, absolute temperature, humidex and wind chill equivalent temperature. Air pressure was defined as mean sea level air pressure in 0.1 hPa. Absolute temperature was measured in degrees Celsius. Humidex is a measure for the temperature adjusted for humidity and was calculated according to the humidex formula by Masterton and Richardson.\textsuperscript{25} Thermal strain in the cold is a combination of ambient temperature and wind speed, expressed in the wind chill equivalent temperature (WCET). WCET was calculated according to the wind chill formula of the National Weather Service.\textsuperscript{26,27}

After ruling out non-linear association by scatter plotting, Spearman’s rank correlation coefficient was used to assess linear correlation between the separate mean absolute climate indices and the incidence of IHPS in both regions according to month and season of birth.

The statistical program R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for Walter and Elwood’s test. All other statistics were performed using the Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL). A \( p \)-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Between 1995 and 2009, 475,941 children were born in North-Holland, of which 612 developed IHPS. In the Northern Netherlands, 287,207 children were born in this period, of which 355 infants were registered with IHPS. Baseline characteristics of the two studied populations are displayed in Table I. Male predominance in both regions was comparable to ratios previously published in literature. The proportion of prematurely born IHPS patients was significantly higher in North-Holland (15.0%) compared to the Northern Netherlands (7.1%), also showing in significant differences in overall birth weight and age at pyloromyotomy between the two populations if not corrected for the prematurity. In both cohorts, the median age at pyloromyotomy was higher in prematurely born infants than in term infants. Term infants were significantly older at surgery in North-Holland than in the Northern Netherlands. When age at pyloromyotomy of preterm infants was corrected for gestational age, no significant differences in median age at surgical procedure remained between the two study groups. Comparison of baseline characteristics between patients recruited from the two different academic centers in North-Holland did not result in any significant difference (data not shown).
Overall incidence of IHPS

The mean overall incidence of IHPS by year of birth was not significantly different between the two study regions: in North-Holland the mean incidence was 1.29 (SE 0.06, 95% CI 1.16 – 1.42) per 1,000 live births and in the Northern Netherlands it was 1.24 (SE 0.07, 95% CI 1.09 – 1.39) per 1,000 live births (p = .62). During the whole study period, fluctuation was seen in the yearly incidence of IHPS within the two regions without a significant difference in incidence between the years (North-Holland $X^2$ 19.5, $p = .146$; Northern Netherlands $X^2$ 13.9, $p = .457$). The highest yearly incidence was found in children born in the year 2000 (1.67/1,000 live births) in North-Holland and in children born in 2008 (1.57/1,000 live births) in the Northern Netherlands (Fig. II).

Monthly and seasonal variations

The highest overall monthly incidence of IHPS was found in children born in December in North-Holland (Fig. III), and in the Northern Netherlands in children born in November.

| Baseline characteristics of all IHPS patients born in the two study regions between 1995 and 2009 |
|---------------------------------------------------|----------------------------------|---------------------|---|
| Total population                                 | North-Holland                   | Northern Netherlands | p-value |
| 2,600,000                                          | 2,500,000                        | 1,700,000            |   |
| Total immigration rate                           | 9.8/1,000                        | 5.9/1,000            |   |
| Total number of live births                      | 475,941                          | 287,207              |   |
| Total percentage prematurely born live births    | 7.0%                             | 7.7%                 |   |
| Number of IHPS cases                             | 612                              | 355                  |   |
| Incidence IHPS / 1,000 live births               | 1.29                             | 1.24                 | ns |
| % males                                          | 86.3%                            | 85.6%                | ns |
| Non-Western origin                               | 13%                              | n/a                  |   |
| Median gestational age (days)                    | 280 (266-280) n=546              | 278 (268-285) n=312  | ns |
| Number preterms (gestational age <37 wks) (%)    | 82/546 (15.0 %)                  | 22/312 (7.1%)        | .001 |
| Mean weight at birth (grams)                     | 3321 (± 682) n=502               | 3448 (± 591) n=313   | .005 |
| Median age at pyloromyotomy (days)               | 32 (25-45) n=612                 | 30 (21-40) n=183     | .002 |
| terms (≥ 37 wks; <42wks)                         | 3492 (± 541) n=426               | 3530 (± 533) n=286   | ns |
| terms + preterms corrected for gestational age to term | 29 (21-39) n=546 | 29 (19-39) n=167    | ns |

IHPS = infantile hypertrophic pyloric stenosis; ns = non significant; n/a = not available. Median values include interquartile ranges in brackets; mean values include standard deviations in brackets.
The Walter and Elwood’s test showed a significant seasonal variation in IHPS occurrence by month of birth in North-Holland with a peak in December (test-value = 10.5, $\theta_{\text{max}} = 5.58$, $p = .005$). No similar seasonality in IHPS incidence was present in the Northern Netherlands. Children born during the winter season in North-Holland showed the highest IHPS incidence rate (1.52/1,000 live births) and in the Northern Netherlands the highest incidence rates was in children born in autumn (1.42/1,000 live births) (Fig. IV). A statistically significant difference between the seasons was present in North-Holland ($X^2 = 6.29$, $p = .012$): the IHPS
incidence in winter was higher compared to summer and spring ($X^2$ 6.29, $p=.012$ and $X^2$ 7.11, $p=.008$, respectively). Redoing these analyses separately for the two academic centers in North-Holland yielded the same results (data not shown). In the Northern Netherlands, no significant differences between the seasons were observed.

**Association with climate indices**

Correlation analysis with climate indices did yield a significant, but weak negative correlation between IHPS incidence by month of birth and mean values of absolute temperature ($r = -.20, p=.006$), humidex ($r = -.20, p=.004$) and wind chill equivalent temperature ($r = -.21, p=.006$) in North-Holland. No such correlations were significant in the Northern Netherlands.

**Discussion**

We report here on the results of an epidemiological study on the incidence of IHPS in two closely located regions in The Netherlands. Due to the location of North-Holland and Northern Netherlands within the Netherlands, separated by a lake (Fig. I), there is no overlap in care to IHPS children in the two regions, despite their close proximity. We found a significant seasonal influence on IHPS incidence in the region North-Holland but not in the region Northern Netherlands. In addition, the seasonal variation in IHPS incidence showed only a weakly negative correlation with several local climate factors such as absolute temperature, humidex and wind chill equivalent temperature for North-Holland. It is unlikely that the observed difference in incidence of IHPS in the various parts of the year in one of the regions has been caused by the climate itself since the climatic differences between the study regions are small, and due to careful and continuous determinations of local climate these small differences could be further corrected for.

The significant peak incidence of IHPS found in children born during the winter months in one of the regions is most in line with the results of a previous study from Belfast investigating seasonal variation in IHPS. Other studies described peak incidences in other parts of the year, or could not demonstrate seasonal variation in the incidence of IHPS at all. The results of previously conducted studies are summarized in Table II.

The current study suggests a role for local environmental influences other than climate changes which are still season specific. These factors may have acted anywhere between the moment of conception and early postnatal life. It may be either completely environmentally determined factors, or environmentally determined factors that act mainly in the presence of a particular genetic constitution. The difference in percentages of immigrants between the two regions may be a factor of influence here, as this indicates a significant difference in genetic constitution between the two regions. In this study, at least 13% of all IHPS patients from North-Holland were children of immigrants. Furthermore,
one may hypothesize that maternal nutrition patterns or medication use because of viral and subsequent bacterial infections varying along the seasons have been such an influence on the development and functioning of the pylorus of the child. This may act either directly or through a change in gene expression by an altered methylation status. Imprinting disturbances are increasingly recognized as having a vast influence on health, not only directly but also by passing the altered imprinting from generation to generation.\textsuperscript{28}

The proportion of prematurely born children with IHPS in North-Holland was more than twice the proportion of prematurely born infants with IHPS in the Northern Netherlands. An explanation might have been the high percentage of immigrants living in North-Holland: studies conducted in the Netherlands have shown that children born to mothers of Non-Western origin are more likely to be born prematurely.\textsuperscript{29,30} However, between 2002 and 2009, the percentage of premature live births in general was found to be remarkably lower in the province of North-Holland (7.0\%) than in the Northern Netherlands (7.7\%).
and the rest of the country (7.3%).\textsuperscript{31} Earlier studies from other countries reported normal to lower rates of prematurity in IHPS patients and therefore, the high percentage of preterm born IHPS children in the province of North-Holland remains remarkable and deserves further investigation.

In neither of the two study regions we found a change in incidence of IHPS over time. In some Northern European countries, a decline in IHPS incidence over the last years has been reported.\textsuperscript{32} Since parents are encouraged to put babies in a supine sleeping position, a comparable decline in the incidence of Sudden Infant Death Syndrome has been observed and it has therefore been suggested that IHPS is related to a prone sleeping position.\textsuperscript{32} This suggested decline in IHPS incidence could not be confirmed in the present study.

The strength of the present study is the large sample sizes of the two studied populations, the relatively long study period, the correction for fluctuations in total number of live births, and the correlation with reliably ascertained local climate data. The ascertainment of IHPS patients in the regions has been very high, confirmed by incidence data in the

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### Table II

<table>
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<tr>
<th>Study Region</th>
<th>Population Definition</th>
<th>Incidence based on</th>
<th>Seasonal variation</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Kwok et al. 1967</td>
<td>USA</td>
<td>Date of admission</td>
<td>+</td>
<td>peak in Spring and Autumn</td>
</tr>
<tr>
<td>Dougall 1969</td>
<td>Scotland</td>
<td>Date of surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Campbell 1969</td>
<td>Hawaii</td>
<td>Date of birth</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dodge 1975</td>
<td>Northern-Ireland</td>
<td>Date of birth</td>
<td>+</td>
<td>peak in Winter</td>
</tr>
<tr>
<td>Adelstein et al. 1976</td>
<td>United Kingdom</td>
<td>Date of birth</td>
<td>+</td>
<td>peak in July</td>
</tr>
<tr>
<td>Kerr 1980</td>
<td>Scotland</td>
<td>Date of birth</td>
<td>?</td>
<td>numbers too small to draw conclusions</td>
</tr>
<tr>
<td>Walpole 1981</td>
<td>Canada</td>
<td>Date of birth</td>
<td>-</td>
<td>-</td>
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<td>Walsworth-Bell 1983</td>
<td>United Kingdom</td>
<td>Date of birth</td>
<td>+</td>
<td>peak in September and October</td>
</tr>
<tr>
<td>Webb et al. 1983</td>
<td>Wales</td>
<td>Date of birth</td>
<td>+</td>
<td>peak in April, low in October</td>
</tr>
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<td>Habbick et al. 1989</td>
<td>Canada</td>
<td>Date of discharge</td>
<td>-</td>
<td>-</td>
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<td>Rasmussen et al. 1989</td>
<td>Denmark</td>
<td>Date of onset symptoms</td>
<td>-</td>
<td>-</td>
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<td>Schechter et al. 1997</td>
<td>USA</td>
<td>Date of discharge</td>
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<td>-</td>
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<td>Sule et al. 2001</td>
<td>Scotland</td>
<td>Date of birth</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Safford et al. 2005</td>
<td>USA</td>
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<td>-</td>
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<tr>
<td>Tiao et al. 2011</td>
<td>Taiwan</td>
<td>Date of birth</td>
<td>-</td>
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<tr>
<td>Leong et al. 2011</td>
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<td>Canada</td>
<td>Date of surgery</td>
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<td>peak in Summer, low in Winter</td>
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</table>
present study regions that are similar to those in earlier studies. For one of the regions (North-Holland) data were gathered separately from the two large academic hospitals and each set of data showed the same results confirming the reliability of the data.

In the near future it will be possible to compare the genetic variation within the various parts of the Netherlands with the results of the Dutch project “Genome of the Netherlands”. In this project, the genome of large groups of trios (child and both parents) from all regions of the Netherlands has been sequenced and will be made available for research purposes. \(^{33}\) We have initiated molecular genetic studies which will also include the study of the methylation of the complete genome (“methylome”) as such methylation change might account for an environmental influence acting through a changed genetic information. These studies and results of studies similar to the study reported here, should shed further light on the etiology of IHPS.

We conclude that there is a remarkable and significant difference in occurrence of IHPS in the various parts of the year in one of the studied populations, in contrast to another closely located independent study population. Climate changes seem unlikely to be the explanation, but there may be other season specific influences such as feeding habits or medication use that have a significant influence. These environmental influences may act independently of or in concert with the genetic make-up of the population, and may also act through changes in imprinting status of genes important for the development of IHPS.

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Reference List


