Artefactual increasing frequency of omphaloceles in the Northern Netherlands: lessons for systematic analysis of apparent epidemics

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Background While monitoring birth defects in a registry, statistically significant increases in prevalence occasionally occur. In the European Registration Of Congenital Anomalies (EUROCAT) in the Northern Netherlands 20 000 births are monitored every year. For omphaloceles, a steady increase in the prevalence from 0.86 per 10 000 live- and stillbirths in 1981–1983 to 3.11 per 10 000 live- and stillbirths in 1994 was seen in the three northern provinces of The Netherlands.

Methods A stepwise enquiry into this increase, which included checking for misclassification and change in coding and ascertainment when necessary, was done. All cases of omphalocele and associated or similar birth defects registered at the EUROCAT registry were retrieved and if necessary recoded.

Results This study showed that the increase reported previously was not a true time trend. A few cases of e.g. diastasis recti and trisomy 18 were misclassified. The prevalence in more recent years is comparable with that in the rest of Europe, whereas it used to be lower. There was an increase in isolated omphalocele, but the numbers are small.

Conclusions The stepwise enquiry described should be a standard procedure after noticing an increasing prevalence in a registry. A better subdivision, e.g. in isolated cases versus children with multiple congenital anomalies, before monitoring can contribute to a lower number of false positive signals.

Keywords Omphalocele, congenital anomalies, monitoring, registries

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In 1981 a register of congenital anomalies was started in the Northern Netherlands (NNL). With 30 other European registries it forms the EUROCAT network (European Registration Of Congenital Anomalies) and with 25 registries from all over the world it forms the mondial network International Clearing-house for Birth Defects Monitoring Systems. A main goal of these 50 registries is to monitor the frequencies of birth defects in many parts of the world. Additional goals include: research on potential risk factors, the evaluation of prevention programmes, and providing public information.

Khoury and Holtzman1 describe, in a study on the ability of birth defect monitoring to detect new teratogens, how a single aetiologic factor may influence a large group of related birth defects, but one very specific birth defect could be strongly associated with one aetiologic factor (e.g. thalidomide and limb reduction defects by an odds ratio of hundreds), whereas the odds ratio for other similar defects is lower. This necessitates the study of grouped birth defects as well as very differentiated defects. For surveillance purposes Khoury and Holtzman advised that birth defect monitoring programmes should classify birth defects into subgroups that are likely to be affected by the same teratogen. These would probably be defects that have a common mechanism or an identical timeframe.1 For many morphological defects however, the aetiology is (partly) unknown, making it difficult to determine these subgroups. Nevertheless, it is possible for instance, to exclude chromosomal anomalies and Mendelian disorders. The present case study may serve as a good example of this principle.

Since the start of the NNL registration, over 4700 children with birth defects have been registered in a population of a total of 200 000 births. In the annual monitoring process of the International Clearinghouse for Birth Defect Monitoring Systems, an increase in the prevalence of omphaloceles was noticed in the NNL registry. Omphalocele is an abdominal wall defect where
there is herniation of viscera into the base of the umbilical cord. The hypothesized development of omphalocele is a failure of embryonic folding at the level of the lateral folds. The total birth prevalence of omphalocles increased from 0.86 per 10 000 live- and stillbirths (n = 2) in 1981–1983, to 1.18 (n = 6) in 1984–1988, to 2.37 (n = 23) in 1989–1993 to 3.11 (n = 6) in 1994. The calculated linear regression coefficient (r = 0.16, P-value = 0.03) indicated a significant increase in the omphalocele rate in the NNL.

When the increase was noted, two important facts were recognized. Firstly, in an earlier study on omphalocles and gastroschisis in Europe the overall prevalence of omphalocles in NNL was lower than in other European regions at that moment. For the most recent period, the prevalence is similar to that in other countries. Secondly, it was noted that several aetiological categories were involved in the increase, such as omphalocele as a symptom of a trisomy or a monogenic disorder and omphalocele as an isolated anomaly. Therefore, a true increase caused by a single aetiological factor was considered unlikely. This article describes the investigation of the background of the observed increase.

Materials and Methods
The data used for this study were collected by EUROCAT NNL over the birth years 1981 through 1995 in the three northern provinces of The Netherlands, with the first of July 1996 as the reference date. In this timeframe the coverage of the registry has increased from 7800 births in 1981 to 19 000 in 1995. The registry receives notifications from various health professionals in the region on a voluntary basis. Since 1992, in order for the infant to be registered, informed consent of the parents must be obtained by the health professional or the registry. In general parents refuse to give consent in 1–2% of cases. Data on children with an omphalocele were mainly first provided by obstetricians (44% of cases), by clinical geneticists (22%) and by paediatricians (15%). Various health professionals can notify the infant to the registry. On average the children with an omphalocele were notified 2.7 times, whereas on the whole children are notified to the EUROCAT NNL registry 1.8 times. The diagnosis of 46% of all infants was verified using a post-mortem report (71% of deceased infants). In a further 27%, a paediatrician diagnosed the infant and notified it to the registry, and in 22% the clinical geneticist saw and diagnosed the infant. There were only three infants that were not examined by one of the professionals mentioned above. Further description of the ascertainment of the NNL registry data can be found in a previous publication.

The usual definition of total birth prevalence is the number of affected livebirths, stillbirths and induced abortions divided by the total number of livebirths and stillbirths in the region. Since some of the cases of omphalocele occurred in spontaneous abortions we included eight spontaneously aborted fetuses with omphalocele (gestational age range 14–23 weeks) in our analyses. The ‘total occurrence’ used in this study is the total birth prevalence in which the spontaneous abortions are included. The definition of stillbirth used by the Central Bureau of Statistics of The Netherlands changed during the study period. The lower gestational age limit shifted from 28 to 24 weeks in 1991. In 1981–1991 6.0 per 10 000 infants born in the region were stillbirths as compared to 5.6 per 10 000 in 1992–1995. The small increase expected in the denominator data is not noticeable.

At the start of the registration, the main purpose was to register the birth defects according to aetiological or pathogenetic background. A trisomy 18, for example, was registered without including all the various symptoms. Later all birth defects, syndromes, and sequences were recorded with all their associated anomalies. The coding of the birth defects varied over the years, but has always been based on the British Paediatric Association/International Classification of Diseases, Ninth Revision (BPA/ICD-9). However, in many cases these codes lacked specificity. Therefore, the EUROCAT network provided each of their members with a EUROCAT extension guide to the BPA/ICD-9 coding in 1990. In this guide birth defects are further specified by adding a digit to the BPA/ICD-9 code. The differences and similarities of the BPA/ICD-9 codes for abdominal wall defects and the EUROCAT extension codes are shown in Table 1. In recent years, the current coding system has also been used to update older data to present standards. This was possible because the written notification forms sent by notifiers were retained.

The present study was performed by retrieving all original notification forms for cases with an isolated omphalocele, Beckwith Wiedemann syndrome, exstrophy of cloaca sequence, trisomy 18, trisomy 13, gastroschisis or an omphalocele, gastroschisis, or umbilical hernia in combination with other congenital anomalies. These syndromes, sequences, and defects were selected because omphalocele is often known to be associated with these anomalies, or because the anomalies are similar to omphalocele and therefore a misclassification of some sort might have occurred. All notification forms were inspected and if necessary, recoded to the current standard.

An omphalocele is considered isolated if there were no other major anomalies present or when there were only anomalies that could be considered consequences of the omphalocele, such as malrotation of the intestines or atresia of the ileum.

Results
A total of 209 566 children were liveborn and stillborn in the region covered by the EUROCAT NNL registry over the years 1981–1995. Of these, 4733 were notified to EUROCAT before July 1996. We retrieved the notification forms of 58 children and fetuses registered with an omphalocele with or without another anomaly. Also, a total of 39 cases of trisomy 18, 26 cases

Table 1 Names, BPA/ICD-9 codes and EUROCATa extension codes for some anomalies of the abdominal wall

<table>
<thead>
<tr>
<th>BPA/ICD-9</th>
<th>EUROCATa extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exomphalos</td>
<td>756.70 Exomphalos/omphalocele 756.701</td>
</tr>
<tr>
<td>Omphalocoele</td>
<td>553.1 Exomphalos/omphalocele 756.701</td>
</tr>
<tr>
<td>Umbilical hernia</td>
<td>553.1 Umbilical hernia 553.1</td>
</tr>
<tr>
<td>Diastasis recti</td>
<td>756.703</td>
</tr>
<tr>
<td>Gastroschisis</td>
<td>756.711</td>
</tr>
</tbody>
</table>

a British Paediatric Association/International Classification of Diseases, Ninth Revision.

b European Registration Of Congenital Anomalies.
of trisomy 13, 17 cases of gastroschisis, eight cases of hernia umbilicalis, seven cases of Beckwith-Wiedemann syndrome, and six cases of extrophy of cloaca sequence were extracted from our files, irrespective of whether they were known to have an omphalocele.

The coding of all cases studied was updated to the present coding protocol by checking the code and adding the EUROCAT extension, or by adding the extra information present on the notification form. In one case of extrophy of cloaca sequence, one case of Beckwith-Wiedemann syndrome and one case of trisomy 18, the omphalocele had not been coded. Two other cases had a diastasis recti, which has a EUROCAT extension code hierarchically included in the BPA/ICD-9 code for omphalocele (76570 for omphalocele; 756703 for diastasis recti). Thus, a total of five cases were misclassified in earlier analyses.

After correction of the five cases mentioned and including two new cases born in 1995, 59 cases of omphalocele were registered during birth years 1981–1995. Of these, 15 were isolated cases of omphalocele (25%). Of the other 44 cases, 13 had a chromosomal aetiology, six cases had a monogenic aetiology, nine had other syndromes, and 16 cases had multiple defects not recognized as a syndrome.

Figure 1 shows the occurrence of omphalocele over the years. There is no statistically significant difference in the total occurrence of all omphaloceles ($\chi^2 = 16.0, P$-value > 0.3).

In Table 2 the different subsets of omphaloceles according to phase of analysis and type of birth are specified for different categories of birth year. Spontaneous and induced abortions are also listed since they were not included in the original analysis by the International Clearinghouse for Birth Defects Monitoring Systems. In the entire group of omphaloceles, there were 35 live births, 12 induced abortions, eight spontaneous abortions, and four stillbirths. When the analyses are done excluding the spontaneous abortions the results do not change. Of the children that were born alive, seven died the same day, and seven died within 10 days. Of the 38 fetuses or children that died, we could verify the diagnosis via post-mortem reports for 27 of them. A further six underwent post mortem, but we had no access to the report. Of the eight spontaneous abortions seven had a post-mortem.

Table 2 The different subsets of the omphalocele cases per categorized year of birth

<table>
<thead>
<tr>
<th>Time period</th>
<th>Total in region</th>
<th>First analysis</th>
<th>Excluded (diastasis recti)</th>
<th>Extra cases</th>
<th>Extra in 1995</th>
<th>Spontaneous abortion</th>
<th>Induced abortion</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981–1983</td>
<td>23 150</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1984–1986</td>
<td>27 287</td>
<td>4</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987–1989</td>
<td>42 535</td>
<td>4</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990–1992</td>
<td>58 628</td>
<td>17</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993–1995</td>
<td>57 966</td>
<td>10</td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>228 599</td>
<td>37</td>
<td></td>
<td>3</td>
<td>2</td>
<td></td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>

\* International Clearinghouse for Birth Defect Monitoring Systems.\(^3\)

\(^1\) Extra cases were: one case with extrophy of cloaca sequence, one case of Beckwith-Wiedemann syndrome and one case of trisomy 18.

\(^2\) Total without 1995 is 38 670.

\(^3\) Total is one less than sum since one of the extra cases was an induced abortion.
In Figure 2, the number of omphalocele cases is given according to recognized condition and specified by type of birth. In the group of multiple congenital anomalies (not depicted in the Figure) there were seven livebirths, three induced abortions, four spontaneous abortions and two stillbirths. In Table 3, the number of cases and prevalences of the various subgroups are shown for timeframes of 5 years. Most prevalences stay relatively stable over the years, but the prevalence of isolated omphaloceles increases significantly over time ($\chi^2 = 4.0$, $P$-value = 0.05) although the numbers are small.

**Discussion**

After studying the increase in omphalocele we conclude that misclassification was the underlying reason for the statistical alarm. After recoding to present standards, thus correcting for misclassification in five cases, the total occurrence of omphaloceles (EUROCAT extension code 756701) no longer shows a clear increase. The total occurrence is 2.82 per 10,000 births. After exclusion of fetal deaths with gestational age <24 weeks, the total birth prevalence is 2.44 per 10,000 births. Calzolari et al.\(^4\) found a total birth prevalence of 2.52 per 10,000 births, with a range from 1.11 in Malta (three cases) to 4.79 in Glasgow (68 cases). This leads us to conclude that the prevalence in NNL is no higher than elsewhere in Western Europe.

When we look at the isolated cases of omphalocele we still see a slight increase which will need further attention. Of the total number of registered omphaloceles, 25% are cases with isolated omphalocele. Calzolari et al.\(^4\) found that 47% of the total omphalocele cases in their European study (excluding EUROCAT NNL cases) were isolated cases. This is a statistically significant difference ($\chi^2 = 10.00$, $P$-value = 0.002). We noted that all infants with isolated omphalocele registered since 1992 were notified (among others) by paediatric surgeons but only few cases before 1992. We therefore verified that no additional cases were known by the paediatric surgeons of the university hospital in the region, the hospital where all cases would be referred to, by checking all discharge letters from 1981 to 1995. This showed that improved ascertainment of relatively mild cases does not appear to play an important role. Maternal age is reported to have some effect on the risk for omphalocele. Young mothers (<20 years) compared to 25–29 year old mothers have a twofold increased risk.\(^4\) In the NNL population the mean maternal age increased during the relevant period from 27.0 in 1981 to 29.6 in 1995. The proportion of mothers under 20 decreased from 3.0% in 1981 to 1.2% in 1995.

Our study clearly illustrates that after observing a statistically significant increase in the frequency of a disorder in registry data, a protocol should be followed in order to consider several
explanations. A first step is to check for a change in coding or classification. Within a registry, there might be different insights over time concerning the coding of the birth defects. Also, the coding system might change. As an example, the transition from ICD-9 to ICD-10 deserves a lot of attention in future registry studies.

A second step is to check for misclassification by ensuring that the right inclusion criteria have been used and that all relevant cases have been checked. It is also important to check for a change in the ascertainment. An increase in frequency of a certain malformation might be caused by an improvement of the diagnostic methods for that malformation. For instance, an increase in the frequency of a certain monogenic disorder could be due to the discovery of a gene for that disorder. This results in improved diagnosis and therefore, higher reporting frequency. Only if, after all these checks, there is still a significant increase, further research into possible causes is indicated.

When we started the investigation of this statistical alarm, we had already noticed that several aetiological categories were involved. Splitting and lumping of morphological defects into categories with a similar aetiology should be done preferably before the start of the monitoring process in order to optimize the power of monitoring birth defects and to avoid false positives. When a morphological defect with several aetiological subgroups is investigated, as in the present study, the risk of getting false positive alarms increases. This is caused by the fact that misclassification, changes in ascertainment or chance effects in all subgroups may influence the monitoring of the morphological defect. To optimize the ability of birth defect monitoring programmes to identify new risk factors, both via optimal power and reducing the risk of false positives, it is therefore essential to classify birth defects in groups that are aetiologically closely related.

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References