Review of gastroschisis on the NSW North Coast

Table of Contents

1. Background

A review of gastroschisis on the NSW north coast was carried out in response to community concerns.

2. Aim

The aims of the review were to:

a. ascertain the number of cases of gastroschisis occurring among residents of the former North Coast Health Area; and

b. Assess whether population-based rates of gastroschisis occurring in the geographic area of interest are higher than expected.

3. Methods

3.1. Study population

The study population was defined as the population resident in the following Local Government Areas (LGAs) on the NSW North Coast: Byron, Ballina, Lismore, Kyogle and Richmond Valley. The study area was chosen because it includes the area in which the newspaper-reported cases reside and also represents a natural community aggregation within the Northern Rivers area of NSW.

In recognition of community concerns about the perceived localised incidence of gastroschisis, analysis was also completed considering only residents of the Lismore LGA.

3.2. Comparison populations

Two comparison populations were selected. First, the remainder of the former North Coast Health Area was selected as active case finding had been carried out for the whole area and it was considered that case ascertainment was complete.

Second, the former Hunter and New England Health Area was selected as it was considered that case ascertainment is likely to be complete—staff from the NSW Register of Congenital Conditions (RoCC) carry out regular active case finding at the John Hunter Hospital, which is a tertiary referral hospital and offers paediatric surgical sub-specialty services. The rate of reported gastroschisis in the Hunter and New England Health Area is higher than other Health Areas reflecting this active case ascertainment (Table 1).

The NSW average prevalence was not considered appropriate for use in comparisons due to concerns about reporting deficiencies in areas where there is not active case ascertainment.

Table 1: Cases of gastroschisis by former health service area of residence NSW 2000-2009

Former health service area of residence	Cases	Total births	Rate per 10,000 births	95% confidence interval	
				Lower bound	Upper bound
Sydney South West	42	202196	2.1	1.5	2.8
South Eastern Sydney & Illawarra	36	148856	2.4	1.7	3.3
Sydney West	29	171170	1.7	1.1	2.4
Northern Sydney & Central Coast	22	138340	1.6	1.0	2.4
Hunter & New England	49	103984	4.7	3.5	6.2
North Coast	11	49875	2.2	1.1	3.9
Greater Southern	3	40744	0.7	0.2	2.2
Greater Western	15	40560	3.7	2.1	6.1
Not Stated/Other	9	8303	10.8	5.0	20.6
All NSW	216	904028	2.4	2.1	2.7

Source: NSW Register of Congenital Conditions, Centre for Epidemiology and Research, NSW Department of Health.

Notes:
1. Includes cases notified as at 31 March 2011
2. In interpreting congenital condition rates among NSW areas, it should be noted that infants with congenital conditions who are born to mothers resident in areas close to interstate borders may be transferred interstate for care and therefore may not be reported to the Register.
3. The Register relies on notifications provided by doctors, hospitals and laboratories in NSW. In addition, records of all cases treated at the three Children's Hospitals in NSW (the Children's Hospital at Westmead, Sydney Children's Hospital, and John Hunter Hospital) are reviewed by Register staff.
4. The reporting of congenital conditions in the Hunter and New England Area is higher than other Areas due to active case finding. If active case finding were carried out in other Areas, it is likely that the rates of gastroschisis would also be higher than reported in the above table.
5. The reported cases in the North Coast in Table 1 do not include cases identified through active case ascertainment

3.3. Cases of gastroschisis

Cases of gastroschisis for the former North Coast Health Area were ascertained from three sources:

a. The NSW Register of Congenital Conditions (RoCC)

b. The NSW Admitted Patient Data Collection (APDC)

Cases that were reported on the APDC and not on the RoCC were verified against the hospital medical record for births in NSW and by Queensland Health for births in Queensland.

c. Queensland Health

Queensland Health verified babies with gastroschisis who were born to mothers resident on the NSW North Coast and were either: born in NSW hospitals and transferred to Queensland hospitals for care; or were born and treated in Queensland hospitals. All babies reported to have been born in Queensland were reported as having gastroschisis on the Queensland Perinatal Data Collection, and all babies treated in Queensland hospitals were reported as having a procedure to correct gastroschisis on the Queensland Admitted Patient Data Collection.

Cases of gastroschisis for the former Hunter and New England Health Area were ascertained from the RoCC.

3.4. North Coast birth population

The birth population was ascertained from two sources:

a. The NSW Perinatal Data Collection for babies born in NSW hospitals to mothers resident on the NSW North Coast.

b. The Queensland Perinatal Data Collection for babies born in Queensland hospitals to mothers resident on the NSW North Coast.

3.5. Statistical analysis

Crude rates of gastroschisis per 10,000 total births (live births and stillbirths) were calculated for three time periods (2000-2005, 2006-2010 and 2008-2010), and three geographic areas (the area of the north coast study population, the remainder of the former North Coast Health Area, and the former Hunter and New England Health Area).

Confidence intervals around the rates were calculated using a Poisson distribution. The proportions of cases of gastroschisis for the remainder of the North Coast and the former Hunter and New England Health Area were compared to the north coast study population using Chi-square and Fisher's exact tests.

Poisson probabilities were used to assess the chance of occurrence of geographic clustering using methods employed in similar analyses of apparent clusters of rare events[1,2].

The results were reviewed by an expert panel.

4. Results

4.1. Statistical analysis considering study population

In the 11-year period 2000 to 2010, a total of 26 cases of gastroschisis were identified among residents of the former North Coast Health Area. Of these, 11 were reported to the RoCC and 15 were identified by active case finding through the NSW Admitted Patient Data Collection and reports from Queensland Health.

Over the same period, a total of 57,765 births occurred to residents of the former North Coast Health Area. Of these, 54,778 (94.8%) births occurred in NSW hospitals and 2,987 (5.2%) births occurred in Queensland hospitals.

Results of the statistical analysis are shown in Table 2. The rate of gastroschisis in the study population is not statistically significantly different to the comparison areas for the years 2000-2005, 2006-2010 and 2008-2010.

Table 2: Occurrence of gastroschisis by study area and comparison areas, NSW 2000-2010

Study area	Cases	Total births	Rate per 10,000 births	95% confidence interval		*p*-value[1]
				Lower bound	Upper bound	
2000-2005						
North Coast study area	2	9602	2.1	0.3	7.5	-
Rest of North Coast	8	20251	4.0	1.7	7.8	0.52
Hunter New England area	28	60550	4.6	3.1	6.7	0.42
2006-2010[2]						
North Coast study area	6	8779	6.8	2.5	14.9	-
Rest of North Coast	10	19133	5.2	2.5	9.6	0.60
Hunter New England area	21	43406	4.8	3.0	7.4	0.45
2008-2010[3]						
North Coast study area	6	5350	11.2	4.1	24.4	-
Rest of North Coast	6	11653	5.2	1.9	11.2	0.17
Hunter New England area	10	21095	4.7	2.3	8.7	0.09

Source: NSW Register of Congenital Conditions and NSW Admitted Patient Data Collection, Centre for Epidemiology and Research, NSW Department of Health.

Notes:

1. For 2000-2005, the *p*-value is the result of a Fisher's exact test of the proportion of cases of gastroschisis in the study population compared to the row comparison group. For 2006-2010, the *p*-value is the result of a Chi-square test of the proportion of cases of gastroschisis in the study population compared to the row comparison group.
2. Data for the Hunter and New England Health Area are for 2006 to 2009.
3. Data for the Hunter and New England Health Area are for 2008 to 2009.

4.2. Statistical analysis considering Lismore cases only

The first case born to a Lismore resident in the eleven year period 2000-2010 occurred in 2008. There were 5 cases born to Lismore residents in the three year period 2008-2010.

From analysis in table 3 (overleaf), there is no evidence of a difference between the rate of gastroschisis in Lismore in the decade 2000-2009 and either the rest of the North Coast or HNE. If the focus is restricted to the period 2006-2010 there is marginal evidence of a difference and further narrowing of attention to 2008-2010 suggests that the rate in Lismore differs significantly from that seen in Rest of North Coast and HNE. Note that this approach to the analysis is incorrect because it arbitrarily 'cherry-picks' a specific location and selected periods from among a larger set of possible location and time period combinations.

Table 3: Occurrence of gastroschisis in Lismore and comparison areas, NSW 2000-2010

Study area	Cases	Total births	Rate per 10,000 births	95% confidence interval		*p*-value[1]
				Lower bound	Upper bound	
2000-2009						
Lismore	3	5399	5.6	1.1	16.2	-
Rest of North Coast[2]	19	46787	4.1	2.4	6.3	0.492
Hunter New England area	49	103984	4.7	3.5	6.2	0.743
2006-2010						
Lismore	5	2831	17.7	5.7	41.2	-
Rest of North Coast[2]	11	25081	4.3	2.1	7.6	0.0180
Hunter New England area[3]	21	43406	4.8	3.0	7.4	0.0192
2008-2010						
Lismore	5	1686	29.7	9.6	69.2	-
Rest of North Coast[2]	7	15317	4.6	1.8	9.4	0.0042
Hunter New England area[4]	10	21095	4.7	2.3	8.7	0.0035

Source: NSW Register of Congenital Conditions and NSW Admitted Patient Data Collection, Centre for Epidemiology and Research, NSW Department of Health.

Note:

1. *p*-value is from Fishers Exact test
2. Rest of NC = all LGAs on North Coast except Lismore
3. Data for Hunter New England are for 2006 – 2009
4. Data for Hunter New England are for 2008 - 2009

4.3. Assessment of likelihood of the occurrence of the observed number of cases by chance alone

The following analysis explores the probability of the occurrence of 5 or more cases of gastroschisis occurring in the Lismore LGA by chance.

Time period 2006-2010

In 2006-2010 there were 5 cases observed in Lismore LGA. Using the Rest of North Coast for the reference population rate, the Poisson probability of 5 or more cases occurring is 0.017634 and hence the probability of this not occurring in Lismore is 1- 0.0017634 = 0.982366. However, Lismore is one of 152 LGAs in NSW, so the probability of not seeing an occurrence this unusual in any LGA is $(0.982366)^{152}$ = 0.0669187. Therefore there is a probability of 93.31% of an event like this, or more extreme, occurring somewhere in one of the LGAs in NSW by chance.

If HNE population is instead used for the reference population rate, this analysis suggests that there is a probability of 58.25% of an event like this, or more extreme, occurring in one of the LGAs somewhere in NSW by chance.

For the time period 2000-2005, the expectation of finding the observed number in Lismore is almost 100%, regardless of the reference population rate used.

Time period 2008-2010

In 2008-2010, there were 5 cases observed in Lismore LGA. Using Rest of North Coast as reference population, the Poisson probability of 5 or more cases occurring is 0.001197 and hence the probability of this not occurring in Lismore is 1- 0.001197 = 0.998803. Lismore is one of 152 LGAs in NSW, so the probability of not seeing an occurrence this unusual in any LGA is $(0.998803)^{152}$ = 0.833535. Therefore there is a probability of 16.65% of an event like this or larger occurring somewhere in one of the LGAs in NSW by chance.

If HNE population is used as reference, this analysis suggests that there is a probability of 19.24% of an event like this, or more extreme, occurring in one of the LGAs somewhere in NSW by chance.

Note that these calculations for this specific time period do not correctly assess the probability of observation of an event like this, or more extreme, in any relevant 3-year period. In this case, a specific 3-year period was selected, but there are a number of possible 3-year periods that could have been chosen to assess case numbers.

If this analysis is extended to consider that 2008-2010 is just one of the 9 possible 3 year periods between 2000-2010, and using the Rest of the North Coast as the reference population, the probability of an event like this not occurring is $(0.998803)^{152x9}$ = 0.19423. Therefore there is a probability of 80.56% of an event like this occurring in an LGA somewhere in NSW in a randomly selected 3 years period. Using HNE as the reference population there is a probability of 85.38% of an event like this occurring in an LGA somewhere in NSW in a randomly selected 3 years period.

5. Conclusion

The observed occurrence of 5 cases in the Lismore LGA in the period 2008-2010 appears to be a random event, which has about a 4 in 5 chance of occurring somewhere across NSW in a three year time interval. This is therefore not an unexpected event, and can be viewed as a normally expected variation in rate over regions and time periods.

6. Expert panel review

An expert panel comprising a toxicologist, paediatric surgeon, perinatal epidemiologist and clinical geneticist considered the results. The panel noted that:

- Gastroschisis is a serious condition that is treatable with surgery and pregnant mothers who have a fetus affected by gastroschisis should be referred to give birth in a hospital with paediatric surgery services readily available. Most babies born with the condition go on to lead a normal healthy life.
- About 3% of babies are born with a congenital condition, such as gastroschisis.
- Over time the incidence of gastroschisis is increasing world-wide and the reasons for this are not known.

- The cause of gastroschisis is not known. Research has shown that risk factors for gastroschisis include young age of the mother (less than 20 years), smoking, and consumption of medications or illicit drugs that are vasoactive (cause blood vessels to constrict). However, in many cases of gastroschisis the baby's mother will have none of these risk factors.
- The epidemiologic evidence for an association between pesticides and herbicides and gastroschisis is poor and unconvincing. A review of the human health effects of atrazine by the Joint FAO/WHO Meeting on Pesticide Residues concluded in 2007 that atrazine was not teratogenic (that is, it does not cause abnormal structures in developing fetuses).
- The rate of gastroschisis in the northern rivers area of NSW (Byron, Ballina, Lismore, Kyogle and Richmond Valley Local Government Areas) is no different to the comparison areas for years 2000-2005, 2006-2010 and 2008-2010.
- The observed occurrence of 5 cases in the Lismore LGA in the period 2008-2010 appears to be a random event, which has about a 4 in 5 chance of occurring somewhere across NSW in a three year time interval. This is therefore not an unexpected event, and can be viewed as a normally expected variation in rate over regions and time periods.
- Research into gastroschisis is currently being carried out in Australia and internationally. An understanding of risk factors in the first 12 weeks of pregnancy is essential to understanding the causes of gastroschisis.

The panel stressed the importance of the mother's health in pregnancy to the health of the baby. Information on planning for a healthy pregnancy can be found from the MotherSafe website at: www.sesiahs.health.nsw.gov.au/mothersafe.

[1] Breast Cancer at the ABC Toowong Queensland Final Report of the Independent Review and Scientific Investigation Panel at http://www.abc.net.au/corp/pubs/documents/Breast_Cancer_Toowong_Final_Report.pdf, June 2007

[2] Coory MD, Wills RA, Barnett AG "Bayesian versus frequentist statistical inference for investigating a one-off cancer cluster reported to a health department", BMC Medical Research Methodology 2009, 9:30

Addendum

Introduction

Following completion of the report concerning the review of gastroschisis on the NSW north coast it became apparent that one of the cases that resides in Kyogle LGA but had been misallocated to the Lismore LGA in earlier analyses. This addendum revisits the probability of observing a cluster of 4 or more cases of gastroschisis in the Lismore LGA. The original report considered the probability of 5 or more cases.

Methods

Study population

The population of interest is the population resident in the Local Government Area (LGA) of Lismore. The analysis was undertaken in recognition of community concerns about the perceived localised incidence of gastroschisis analysis within the Lismore LGA.

Comparison populations

This analysis uses the same two comparisons populations used in the original report for this part of the analysis. That is, all other LGAs of the former North Coast Area Health and the former Hunter and New England Health Area. These areas were chosen as comparisons because of the comparable completeness of case ascertainment.

Results

The first case born to a Lismore resident in the eleven year period 2000-2010 occurred in 2008. There were 4 cases born to Lismore residents in the three year period 2008-2010.

Table A.1 shows the rate of gastroschisis in the Lismore population and comparison areas for the years 2000-2009, 2006-2010 and 2008-2010 and indicates that there is no evidence of a difference between the rate of gastroschisis in Lismore in the decade 2000-2009 and either the rest of the North Coast or HNE. If the focus is restricted to the period 2006-2010 there is marginal evidence of a difference (p values close to 0.05) and further narrowing of attention to 2008-2010 suggests that the rate in Lismore may differ significantly from that seen in Rest of North Coast and HNE (that is, $p < 0.05$). Note that this approach to the analysis is incorrect because it arbitrarily 'cherry-picks' a specific location and selected periods from among a larger set of possible location and time period combinations.

The following analysis explores the probability of the occurrence of 4 or more cases of gastroschisis occurring in the Lismore LGA by chance.

Table A.1: Occurrence of gastroschisis, Lismore LGA and comparison areas, NSW 2000-2010

Study area	cases	births	Rate per 10,000 births	95% confidence interval		*p*-value[1]
				Lower bound	Upper bound	
2000-2009						
Lismore	2	5399	5.6	1.1	16.2	-
Rest of North Coast[2]	19	46787	4.1	2.4	6.3	0.492
Hunter New England area	49	103984	4.7	3.5	6.2	0.743
2006-2010						
Lismore	4	2831	14.1	3.8	36.2	-
Rest of North Coast[2]	12	25081	4.7	2.4	8.1	0.0713
Hunter New England area[3]	21	43406	4.8	3.0	7.4	0.0634
2008-2010						
Lismore	4	1686	23.7	6.5	60.7	-
Rest of North Coast[2]	8	15317	5.2	2.3	10.3	0.0249
Hunter New England area[4]	10	21095	4.7	2.3	8.7	0.0164

Source: NSW Register of Congenital Conditions and NSW Admitted Patient Data Collection, Centre for Epidemiology and Research, NSW Department of Health.

Notes:

1. The *p*-value is from Fisher's exact test of cases of gastroschisis in the study population compared to the row comparison group.
2. Rest of North Coast = all LGAs on North Coast except Lismore
3. Data for the Hunter and New England are for 2006 to 2009
4. Data for the Hunter and New England are for 2008 to 2009

Time period 2006-2010

In 2006-2010 there were 4 cases observed in Lismore LGA. Using the Rest of North Coast for the reference population rate, the Poisson probability of 4 or more cases occurring is 0.082664 and hence the probability of this not occurring in Lismore is 1- 0.082664 = 0.917336. However, Lismore is one of 152 LGAs in NSW, so the probability of not seeing an occurrence this unusual in any LGA is $(0.917336)^{152}$ = 0.000002. Therefore there is a probability of over 99.9% of an event like this, or more extreme, occurring somewhere in one of the LGAs in NSW by chance. If HNE population is instead used for the reference population rate, this analysis suggests that there is a probability of 98.4% of an event like this, or more extreme, occurring in one of the LGAs somewhere in NSW by chance.

Time period 2008-2010

In 2008-2010, there were 4 cases observed in Lismore LGA. Using Rest of North Coast as reference population, the Poisson probability of 4 or more cases occurring is 0.012522 and hence the probability of this <u>not</u> occurring in Lismore is 1- 0.012522 = 0.987478. Lismore is one of 152 LGAs in NSW, so the probability of <u>not</u> seeing an occurrence this unusual in any LGA is $(0.987478)^{152}$ = 0.1472996. Therefore there is a probability of 85.27% of an event like this or larger occurring somewhere in one of the LGAs in NSW by chance.

If HNE population is used as reference, this analysis suggests that there is a probability of 74.82% of an event like this, or more extreme, occurring in one of the LGAs somewhere in NSW by chance. So, this suggests that there is a 4 in 5 chance of an event like this, or larger, occurring in an LGA somewhere in NSW by chance

Note that these calculations for this specific time period do not correctly assess the probability of observation of an event like this, or more extreme, in any relevant 3-year period. In this case, a specific 3-year period was selected, but there are a number of possible 3-year periods that could have been chosen to assess case numbers.

If this analysis is extended to consider that 2008-2010 is just one of the 9 possible 3 year periods between 2000-2010, and using the Rest of the North Coast as the reference population, the probability of an event like this not occurring is $(0.987478)^{152x9} < 0.000001$. Therefore there is a probability of more than 99.9% of an event like this occurring in an LGA somewhere in NSW in a randomly selected 3 years period. Using HNE as the reference population produces similar results, indicating that is almost inevitable that an event like this, or more extreme, would occur in an LGA somewhere in NSW in a randomly selected 3 years period.

Conclusion

The observed occurrence of 4 or more cases in the Lismore LGA in the period 2008-2010 appears to be a random event, which will almost inevitably occur somewhere across NSW in a three year time interval. This is therefore not an unexpected event, and can be viewed as a normally expected variation in the rate over regions and time periods.