Esophageal atresia and tracheo-esophageal fistula in Western Australia: prevalence and trends

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Conflicts of Interest and Source of Funding
This work and EL were funded by an Australian National Health and Medical Research Council (NHMRC) Program Grant (#572742). CB was supported by a NHMRC Principle Research Fellowship (#634341) and NN by a NHMRC Career Development Fellowship (#632955). There are no financial or other relationships that might lead to a conflict of interest with the study.
Abstract

Objectives

A recent international study reported a higher prevalence of esophageal atresia with or without tracheo-esophageal fistula (EA±TEF) in Western Australia (WA). The aim of this study was to examine the prevalence and trends of EA and/or TEF in WA; determine the proportion of cases with associated anomalies; and explore the impact of time of diagnosis.

Methods

The study population comprised all infants born in WA, 1980-2009 and registered with EA and/or TEF on the WA Register of Developmental Anomalies (WARDA).

Results

EA±TEF and TEF alone affect, on average, 1 in every 2,927 births in WA, with a total prevalence of 3.00 and 0.42 per 10,000 births, respectively. The prevalence of EA±TEF increased by 2.0% per annum, with only cases with associated anomalies (64% of cases) demonstrating an increase. TEF rates were stable. Among EA±TEF infants, the proportion of live births, stillbirths and elective terminations of pregnancy for fetal anomaly (TOPFA) was 79%, 6% and 15%, respectively; while the majority (94%) of TEF only cases were live births. In 2000-2009 there was 30% fall in EA±TEF live births with 61 (58%) cases diagnosed in first week of life, 10 (9%) prenatally and 34 (32%) at postmortem only.

Conclusions

A higher prevalence of EA±TEF in WA was observed with increase over time attributable to increase with associated anomalies. Consistent reporting, availability of prenatal diagnosis and ascertainment of cases following TOPFA or postmortem examinations can significantly affect prevalence of EA and/or TEF.

Keywords

esophageal atresia, tracheo-esophageal fistula, prevalence, pregnancy, epidemiology
INTRODUCTION

Esophageal atresia and tracheo-esophageal fistula are the most common anomalies of the esophagus and trachea. Esophageal atresia is a congenital anomaly of the upper gastrointestinal tract characterized by the complete discontinuity of the esophagus with or without an abnormal connection between the esophagus and the trachea (EA±TEF). Tracheo-esophageal fistula (TEF) can also occur without esophageal atresia and accounts for 7-18% of all congenital tracheo-esophageal malformations. Infants are diagnosed either prenatally or, in most cases, at birth and require surgical repair in the first few days of life. The etiology of EA and/or TEF is still unclear and is considered to be multifactorial.

Large variations in prevalence of EA±TEF across different geographical regions have been reported, although no changes in prevalence over time have been observed. The overall prevalence of EA±TEF in 23 European registries of congenital anomalies during 1987-2006 was 2.43 per 10,000 births, ranging from 1.27 to 4.55, with no differences in the prevalence over time. The estimated national prevalence of EA±TEF reported by the US National Birth Defects Prevention Network, based on data from 14 population-based birth defects registries, was 2.17 per 10,000 births for the period from 2004 to 2006. For this study, cases included EA and/or TEF and esophageal stenosis. Similarly, a recent international study among 18 birth defects surveillance programs in Europe, the Americas and Australia reported an overall prevalence of EA±TEF of 1 in 4,099 (2.44 per 10,000) births. Although there was no evidence of a significant linear trend among any of the member programs, there was both a higher prevalence, particularly of TEF alone, and increase in cases in Western Australia during the period of study, 1998 to 2007.

Several factors may influence reporting and registration of congenital anomalies including: screening policies and procedures, clinician skills, timing of fetal anomaly screening, subsequent availability and timing of elective termination of pregnancy, and autopsy policies. Thus, a number
of factors may explain the higher observed rates of EA and/or TEF in Western Australia; including multiple sources of notification, inclusion of cases following termination of pregnancy or post-mortem examinations, availability of prenatal diagnosis and higher age of registration up to six years. Only tabulated data were available for the international study. Individual information regarding timing and age of diagnosis, specific source of notification, whether cases were isolated or associated with multiple anomalies and whether there have been changes in diagnosis and reporting over time would provide further insight regarding ascertainment and reporting of cases, and possibly the underlying etiology of these conditions.

The frequency of additional anomalies in previous population-based investigations reporting EA and/or TEF have ranged between 43 and 63%. Congenital heart disease is the most commonly associated congenital anomaly and the proportion reported with chromosomal anomalies is 5-10%. EA and/or TEF are more likely to be diagnosed in conjunction with many syndromes, sequences and associations; with the most common being VACTERL association.

The aim of this study was to examine the birth prevalence and trends of EA and/or TEF in Western Australia; determine the proportion of cases with isolated and multiple anomalies; and explore the impact of different sources and timing of diagnosis on rates.
METHODS

Western Australia is a geographically well defined area, with a population of 2.3 million, the majority of whom live in the Perth metropolitan area. There are approximately 31,000 births per year. Cases of EA and/or TEF were identified from the Western Australian Register of Developmental Anomalies (WARDA), a population-based notification system of malformations established in 1980.\textsuperscript{11} The WARDA draws on multiple sources of notification including hospitals and private practitioners, Western Australian Department of Health databases (midwives’, mortality and hospital morbidity systems) and investigative and treatment centers. All fetuses and neonates diagnosed with EA and/or TEF in Western Australia from January 1980 to December 2009 inclusive, were identified from the WARDA, including stillbirths of 20 weeks’ gestation or more, terminations of pregnancies for fetal anomaly of any gestation (TOPFA) and live born children up to six years of age. Timing and age of diagnosis was also identified and may have been prenatally from antenatal ultrasound, in first few weeks of life or later or at post mortem.

Each individual birth defect is coded by the WARDA according to the British Paediatric Association International Classification of Diseases, 9\textsuperscript{th} revision system (BPA-ICD9), with up to ten diagnostic categories available to allow coding of multiple anomalies per case. The following codes were used to identify the diagnosis of EA: 750.30, EA+TEF: 750.31; and TEF alone: 750.32. All records were reviewed and classified into one of four groups as: 1) isolated cases, if EA±TEF or TEF alone were the only defects present; 2) cases with non-syndromic multiple congenital anomalies when one or more additional non-esophageal malformations were recognized; 3) cases with non-chromosomal recognized conditions including syndrome, sequence, association and spectrum disorders; and 4) cases with chromosomal anomalies. Congenital anomalies in cases with non-syndromic multiple anomalies were also classified by organ system.
Total birth prevalence (and 95% confidence interval) and trends over time of EA±TEF and TEF, and by birth outcome and age at diagnosis were examined. Birth prevalence was defined as the total number of cases among live births, stillbirths and TOPFA divided by the sum of live births and stillbirths in the Western Australia population and expressed per 10,000 births. Denominator data were obtained from the Western Australia Department of Health and consisted of all live births and stillbirths of 20 weeks’ gestation or more born in Western Australia. Annual, decade-specific (1980-1989, 1990-99, 2000-2009) and overall prevalence were calculated. The Cochran-Armitage test\textsuperscript{21} was used to evaluate homogeneity and time trend in prevalence for EA±TEF and TEF alone, in both isolated cases and cases with associated anomalies. To allow for rare events and variation in births over time, Poisson regression with an offset term was used to assess the trend and calculate the average annual change in prevalence over the study period. Prevalence was also examined by birth outcomes classified as live births, stillbirth or TOPFA; and age at first diagnosis (prenatal, within first week of life, after first week of life, postmortem). Statistical analyses were performed using Stata 11.2 (Stata Corporation, College Station, TX). Ethics approval for access to data and to conduct the study was obtained from the Western Australian Department of Health Human Research Ethics Committee.
RESULTS

A total of 260 cases of EA and/or TEF were notified to the WARDA out of 761,247 births in the 30-year period from 1980-2009, yielding an overall prevalence of 3.42 cases per 10,000 births (95%CI 3.01-3.86). Annual number of births increased from approximately 21,000 in 1980 to 31,000 in 2009. Of the 228 EA±TEF cases (3.00 per 10,000 births; 95%CI 2.62-3.41), EA with TEF comprised 202 (89%) of the cases and 26 (11%) had EA without TEF. The percentage of EA alone decreased over the three decades (14.8%, 9.8%, and 10.4% for 1980-1989, 1990-1999 and 2000-2009, respectively). The proportion and trend in the prevalence of EA±TEF increased, on average, by 2.0% per year (95%CI 1.0-4.0%, P<0.01) from 2.23 (95%CI 1.66-2.92) to 2.16 (95%CI 1.63-2.81) to 3.48 per 10,000 births (95%CI 2.82-4.26) over the three decades, respectively (Figure 1).

There were 32 cases of TEF alone identified in Western Australia, 1980-2009 resulting in a prevalence of 0.42 per 10,000 births (95%CI 0.29-0.59). Despite the small numbers, the trend in the prevalence of TEF alone was relatively stable over time (P=0.98) (Figure 1).

Among the 228 cases of EA±TEF, 180 resulted in a live birth (79%, 2.36 per 10,000 births), 14 (6%) were stillbirths and 34 (15%) were TOPFA. Over the three decades, the proportion of livebirths decreased by a third to 66%, while in 2000-2009, 9% of cases diagnosed were stillbirths and almost a quarter (24%) were TOPFA. In contrast, the majority of cases of TEF alone were livebirths (n=30, 94%).

In 2000-2009, there were 60 (63%) cases of EA+TEF cases diagnosed in the first week of life, most of them at birth. In 7 cases (7%) the diagnosis was made prenatally, in 1 case (1%) after the first week of life, and in 27 cases (28%) the diagnosis was first made postmortem (Table 1). In contrast, two-thirds (64%) of EA alone were first diagnosed at postmortem. Table 1 highlights the increase in prenatal detection and postmortem diagnoses for EA±TEF cases over the study period, with a
corresponding decrease in the proportion of cases diagnosed in first week of life. During 2000-2009, the majority (82%) of TEF only cases were diagnosed in first week of life, 9% prenatally and 9% after the first week.

Only one-third (n=72, 36%) of EA+TEF cases were isolated and the remaining 130 had associated anomalies; including 21 (10%) with chromosomal abnormalities, 50 (25%) had non-chromosomal recognized conditions, of which 40 (20%) were diagnosed with VACTERL association, and 59 (29%) had non-syndromic multiple congenital anomalies (Table 2). The most common additional structural anomalies were those of the cardiovascular and musculoskeletal system, present in 17.8% and 11.4% of cases, respectively. Infants diagnosed with EA alone had a similar proportion of non-syndromic and non-chromosomal conditions, but a lower proportion were isolated (19%) and a higher percentage were diagnosed with chromosomal anomalies (n=6, 23%), but numbers were small (Table 2). Of the 32 cases of TEF alone, 17 were isolated (53%), 6 (19%) had multiple anomalies and 7 (22%) had a VACTERL association (Table 2).

For all cases of EA±TEF, the total prevalence of isolated cases was 1.01 per 10,000 births (95%CI 0.80-1.26); increasing slightly from 1.03 (95%CI 0.66-1.53) in 1980-89 to 1.25 per 10,000 births (95%CI 0.86-1.74) in 2000-09 (P=0.17) (Figure 2). For cases with associated anomalies the overall prevalence was 1.98 (95%CI 1.68-2.33) per 10,000 births; increasing, on average, by 3.0% per annum (P<0.01) from 1.58 (95%CI 1.12-2.18) to 1.65 (95% CI 1.19-2.23), and 2.64 per 10,000 (95%CI 2.07-3.32) over the study decades (Figure 2). Overall, the ratio of isolated to associated anomalies did not vary significantly or show a trend across the three time periods (ratio 0.65 in 1980-89, 0.45 in 1990-99, and 0.47 in 2000-09).
DISCUSSION

EA±TEF and TEF alone affect, on average, 1 in every 2,927 births in Western Australia, with a total prevalence of 3.00 for EA±TEF and 0.42 for TEF alone per 10,000 births. The prevalence of EA±TEF in Western Australia has increased by 2% per annum over the 30-year period, from 1980 through 2009. However, when cases were subdivided by isolated and associated anomalies, only the associated EA±TEF group demonstrated a significant increase. Furthermore, results reveal that there was a 30% fall in live birth cases offset by an increase in the proportion of cases diagnosed following stillbirth or TOPFA.

In this study we found a higher prevalence of EA±TEF (3.42 per 10,000) compared to that reported in three recent studies; of 2.44 per 10,000 births by the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR),10 2.46 per 10,000 births by EUROCAT, the European surveillance of congenital anomalies8 and 2.17 per 10,000 births by the National Birth Defects Prevention Network in the US.9 Findings suggest increased case ascertainment in Western Australia with additional information obtained from post mortem reports most likely to explain higher rates. The prevalence reported in this study is also higher than that reported for Western Australia in the ICBDSR study (2.63 per 10,000 births)10 and is due to a misclassification of TEF alone, which were identified on post mortem to also have EA.

Our findings reveal one-quarter of EA±TEF and TEF to be associated with non-chromosomal recognized conditions, considerably higher than rates of around 7-17% found in previous studies.4 8 The most common associated anomaly was VACTERL association which was present in about 20% of cases, with the percentage the same in patients with EA±TEF and TEF alone. The reported percentage of VACTERL association in patient with EA and/or TEF in population-based studies varies, ranging from 2-10%,4 8 19 however, studies from single institutions report either a similar percentage to our finding22 or higher.23
Although we found an increasing prevalence of EA±TEF over the 30-year period, 1980-2009, this trend was observed in non-isolated cases only. No overall change in trends was observed in the EUROCAT study during 1987-2006\(^8\) or the ICBDSR study for 1998-2007.\(^{10}\) Our results suggest that the causative factors are due to either increased reporting and ascertainment; or attributable to underlying etiological factors affecting embryonic fetal development more generally and are not just restricted to the gastrointestinal system. An increase in ascertainment of cases over time may be one factor contributing to both the higher proportion of and rising trend of EA±TEF with associated anomalies. However, given the WARDA has multiple sources of notification with no major change in data collection or registration of cases over the last 30 years; and that esophageal anomalies are a serious condition, diagnosed early in life, it is unlikely these cases will be missed, and increasing trends may be real.

Findings highlight increasing proportion of cases diagnosed following termination of pregnancy for fetal anomaly and following post mortem resulting from improved availability, ascertainment and reporting of these occurrences. Previous studies have shown that the rate of termination of pregnancy is higher for cases with chromosomal or additional congenital anomalies than for cases with an isolated anomaly.\(^{12}\) Increases in the prevalence of chromosomal and syndromic anomalies diagnosed over the last few decades may be a result of increased detection and reporting in Western Australia with higher proportion of all types of associated anomalies; including chromosomal, non-chromosomal and non-syndromic anomalies diagnosed compared with previous reports.\(^{1,4,8,14-20}\)

This is also affirmed by our finding of higher rates of stillbirths and terminations of pregnancies among cases, which are more likely to occur among those with associated anomalies and availability of ascertainment via prenatal diagnosis, postmortem assessment and ample period of follow-up.\(^{24}\) In addition, the WARDA also assign age at diagnosis for each specific anomaly diagnosed in each infant compared with other studies that classify an overall or first time of
diagnosis. For example, those cases terminated for chromosomal anomaly will have that specific anomaly diagnosed prenatally; while an esophageal anomaly diagnosed post mortem will be assigned as such. This may explain our higher proportion of cases diagnosed post mortem (20%) and fewer prenatally (8%) compared with EUROCAT study reporting a 33% prenatal detection rate.8

An increase in underlying etiological factors associated with chromosomal and non-chromosomal syndromes or associations, in general, may also be implicated. Potential factors attributed to their rise have also been linked with increased risk of esophageal defects and include older maternal age,16 25 maternal medical conditions,26-28 and multiple pregnancies. Of interest is a recent study demonstrating a consistent association between pre-gestational diabetes and cases with esophageal defects and associated congenital anomalies, irrespective of maternal BMI.27 Greater use of assisted reproductive technology (ART) over the last 20 years may have also contributed to the increasing prevalence. ART is associated with increased risk of birth defects compared with births from spontaneous conception.29-34

Due to limited data, we were unable to explore the association and contribution of these and other parental, genetic and environmental factors to rates and trends of EA±TEF in Western Australia, all of which require thorough assessment in future studies. Despite the increase in associated anomalies, we found the ratio of isolated to associated anomalies (~0.45) did not change over the last 20 years. An unequal distribution in esophageal defects was previously reported3 35 36 but not in the study by Torfs et al.,4 where the proportion of associated anomalies didn't vary substantially between esophageal defects. One of the key explanations for the unequal distribution was attributed to delay in diagnosis.36 However, given the WARDA includes anomalies diagnosed up to the age of 6 years, this hypothesis is not valid for this setting.11 24
In regards to the prevalence of TEF alone, results in the present study do not differ significantly from the reported prevalence in the literature. Three US studies reported the prevalence of TEF to be between 0.16 and 0.52 per 10,000 births,\(^4\)\(^{14}\)\(^{37}\) EUROCAT found a prevalence of 0.26 in 6 centers,\(^1\) and the ICBDSR\(^10\) showed a total prevalence of 0.22 per 10,000 births. Although the Western Australian prevalence reported in the latter study was high (1.3 per 10,000 births) this has now dropped due to the review and additional diagnosis of EA from post mortem reports and reclassification of cases to EA±TEF. A much lower proportion of associated anomalies was also observed in infants with TEF without atresia.

The strengths of this study are that it is a population-based study with prospective data collection and congenital anomalies diagnosed prenatally and up to the age of 6 years are included.\(^{11}\)\(^{24}\) The WARDA uses multiple sources for active case ascertainment and cases comprise anomalies occurring in live births, stillbirths and in pregnancies terminated because of fetal anomaly. Given that esophageal defects are more likely to be diagnosed in conjunction with other anomalies as chromosomal, syndromes, associations or multiple anomalies without a pattern,\(^2\)\(^3\)\(^{20}\) that may result in termination of pregnancy, a complete ascertainment of all terminations for fetal anomaly as well as an accurate postmortem diagnosis is also necessary to provide reliable baseline data on the prevalence of esophageal defects. This comprehensive approach is demonstrated when comparing our prevalence of EA±TEF (3.42) with that from a recent national French study, reporting a rate of 1.8 per 10,000 births where only live birth cases were included.\(^{13}\)

In summary, we found a higher and increasing prevalence of EA±TEF diagnosed in Western Australia over the last 30 years compared with studies elsewhere. Findings suggest the trend is attributable to an increase in the proportion of infants with associated anomalies, particularly chromosomal and non-chromosomal cases with an association or syndrome. Separating effects of increased prevalence attributable to improved reporting and ascertainment of associated anomalies
and underlying etiological factors is difficult, but important. Future studies disentangling and taking these factors into account are essential to contribute to our understanding of the underlying etiology and impact of esophageal anomalies.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the valuable work of the WARDA staff, Edwina Rudy, Ann Callaghan, Jennifer Quick, and Alison Rowley; and thank Peter Cosgrove for his assistance with database management.
REFERENCES


Figure legend

Figure 1 - Prevalence of esophageal atresia without (EA) or with tracheo-esophageal fistula (EA+TEF) and tracheo-esophageal fistula without esophageal atresia (TEF), Western Australia, 1980-2009
Figure 2 - Prevalence of cases with associated anomalies and isolated cases of esophageal atresia with or without tracheo-esophageal fistula in Western Australia, 1980-2009

Table 1: Number (%) of cases of esophageal atresia without (EA) or with tracheo-esophageal fistula (EA+TEF) and tracheo-esophageal fistula without esophageal atresia (TEF) in Western Australia, 1980-2009 by age at diagnosis

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>EA (N=26)</th>
<th>EA+TEF (N=202)</th>
<th>TEF (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Prenatally</td>
<td>0 (0)</td>
<td>1 (17%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Within the first week of life</td>
<td>7 (78%)</td>
<td>3 (50%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>After the first week of life</td>
<td>1 (11%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>At post-mortem examination</td>
<td>1 (11%)</td>
<td>2 (33%)</td>
<td>7 (64%)</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>1 (8%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Table 2: Classification of esophageal atresia without (EA) or with tracheo-esophageal fistula (EA+TEF) and tracheo-esophageal fistula without esophageal atresia (TEF) cases, Western Australia, 1980-2009

<table>
<thead>
<tr>
<th></th>
<th>EA (n=26)</th>
<th>EA+TEF (n=202)</th>
<th>TEF (n=32)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>95% CI</td>
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<tr>
<td>Isolated</td>
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<td>19.2</td>
<td>(8.5-37.9)</td>
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<tr>
<td><strong>Non-syndromic associated anomalies (*)</strong></td>
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<tr>
<td>Cardiovascular</td>
<td>8</td>
<td>30.8</td>
<td>(16.5-50.0)</td>
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<tr>
<td>Digestive</td>
<td>3</td>
<td>11.5</td>
<td>(4.0-29.0)</td>
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<tr>
<td>Central nervous system</td>
<td>2</td>
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<td>(2.1-24.1)</td>
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<td>Head and face</td>
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<td>0.0</td>
<td>(0.0-12.9)</td>
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<td>Respiratory system</td>
<td>0</td>
<td>0.0</td>
<td>(0.0-12.9)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0.0</td>
<td>(0.0-12.9)</td>
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<tr>
<td><strong>Non-chromosomal recognized conditions</strong></td>
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<tr>
<td>VACTERL association</td>
<td>4</td>
<td>15.4</td>
<td>(6.1-33.5)</td>
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<td>Oculo-auriculo-vertebral spectrum</td>
<td>0</td>
<td>0.0</td>
<td>(0.0-12.9)</td>
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<td>Caudal dysplasia</td>
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<td>(0.0-12.9)</td>
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<tr>
<td>Prune-belly sequence</td>
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<td>3.8</td>
<td>(0.7-18.9)</td>
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<td>Sirenomelia</td>
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<td>3.8</td>
<td>(0.7-18.9)</td>
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<td>Charge syndrome</td>
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<td>(0.0-12.9)</td>
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<td>Meckel Gruber syndrome</td>
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<td>(4.0-29.0)</td>
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<tr>
<td>Edward syndrome (Trisomy 18)</td>
<td>2</td>
<td>7.7</td>
<td>(2.1-24.1)</td>
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<tr>
<td>Other chromosomal abnormalities</td>
<td>1</td>
<td>3.8</td>
<td>(0.7-18.9)</td>
</tr>
</tbody>
</table>

(*) Numbers do not add to total as a case may have more than one associated congenital anomaly diagnosed