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Epidemiology of Robin sequence with cleft palate in the East of Scotland between 2004 and 2013

Running Title: Robin Sequence Epidemiology - UK retrospective study.

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ABSTRACT

Background: Robin sequence (RS) is a congenital disorder characterised by cleft palate, micrognathia, and glossoptosis which can result in clinically significant upper airway obstruction (UAO). Historically, incidence of RS in the UK has been estimated as 1 in 8500 live births. Our study describes birth prevalence, clinical characteristics, and management of RS in the East of Scotland (EoS) region.

Methods: Retrospective case note review of infants born in EoS from 2004-2013 with a clinical diagnosis of RS. Cases were identified by searching the regional cleft service patient database and review of Hospital Activity Statistics data. Regional live birth rate provided the denominator for incidence calculations.

Results: 105 cases of RS were identified, giving a birth prevalence of 1:2685 live births. No trends in annual incidence were observed over the 10-year period. Intrauterine exposure to potentially teratogenic agents was identified in 17% cases, including Methadone in 8% cases. Signs of UAO were present in 93% of infants, 63% of whom required active airway management. Nasopharyngeal airway (NPA) was the most commonly used intervention (53% cases), whilst only 7% required surgical management.

Conclusions: RS incidence in EoS is substantially higher than that reported within other populations, and than previously reported in the UK. A possible association with intrauterine Methadone exposure warrants further investigation. A national surveillance study is underway to investigate RS incidence across the United Kingdom.

INTRODUCTION

Robin Sequence (RS) is a congenital disorder in which impaired mandibular growth in the first trimester of pregnancy leads to an abnormally posterior tongue position (glossoptosis) and failure of palatal shelf closure (cleft palate). Together, these features cause a narrowing of the pharynx which can result in upper airway obstruction and feeding difficulties. Affected infants are at risk of faltering growth secondary to feeding difficulties and increased calorie utilisation from work of breathing. Furthermore, there are postulated effects on development relating to sleep fragmentation if airways obstruction is untreated. Initial hospital stays can be lengthy whilst symptoms are monitored, airway and feeding adjuncts are introduced, and caregivers are trained in their use.

The incidence of RS is reported to be between 1:8,850 to 1:14,000 live births, based on data from national studies conducted in Germany and Denmark.^{1,2} The most recent study of RS epidemiology in the UK, published over 30 years ago, similarly reported RS incidence as 1 case per 8500 live births.³ However, more recently data from USA and The Netherlands suggest that RS may be more common than previously suggested, with an estimated RS birth prevalence of 1 case per 3130 to 5600 live births reported.^{4,5}

We hypothesised that the incidence of RS in the UK had increased since last reported. The study was designed to address this research question, and reports RS incidence in the East of Scotland (EoS) from 2004-2013. We also describe the airway management of infants with RS

at our centre, where a multidisciplinary team involving respiratory and cleft specialists adopt a shared care approach to RS management.

MATERIALS AND METHODS:

During the study period, the cleft service based at the Royal Hospital for Sick Children (RHSC) in Edinburgh managed children with orofacial clefts across the EoS area incorporating six Scottish NHS Boards (NHS Lothian, Borders, Fife, Tayside, Grampian and Highland). All affected children were reviewed by a Cleft Clinical Nurse Specialist within 72 hours of diagnosis, and this assessment specifically included examination for features of RS. Medical records of all infants registered on the RHSC cleft database born between January 2004 and December 2013 were reviewed to delineate the cohort with a diagnosis of RS. Clinical coding data were separately obtained for all admissions to the RHSC over the same period with ICD-10 codes relating to craniofacial abnormalities, and medical records of these children were also reviewed for a diagnosis of RS. The case definition of RS used for study eligibility was the presence of all of the following clinical features: (1) cleft palate; (2) glossoptosis; (3) micro- or retrognathia. This definition is reflective of the diagnostic criteria most commonly used by both European and North American clinicians involved in RS management.^{6,7} Children born within the RHSC catchment area but later moving to another region or receiving care from a different cleft service were included in the study to ensure accuracy of birth prevalence calculations. Similarly, children born outside of the included NHS Boards but followed up at RHSC were excluded from analysis.

Incidence rates were calculated using annual live birth rates in each EoS NHS Board as a denominator, which were obtained from the General Register Office for Scotland (now National Records of Scotland).⁸

Clinical data were collected (where available) from the medical records of affected infants, including maternal and antenatal history, family history of RS or related syndromes, clinical presentation, methods of airway and feeding management utilised, and duration of initial hospital admission. Limited follow-up data were recorded, including duration for which airway and feeding adjuncts were required.

Statistical analyses were performed using SPSS Statistics v23.0 for Windows (IBM Corp., NY, USA) and GraphPad Prism v-6 for Windows (GraphPad Software, La Jolla California, USA). Differences between groups were calculated using χ^2 or Fisher's exact tests for categorical data and one-way ANOVA for continuous data, with a p-value of <0.05 considered statistically significant.

The study had ethical approval (South East Scotland REC, 13/SS/0238) and was also approved by the Caldicott Guardian national scrutiny panel (NRS14/PE76).

RESULTS

A total of 281 885 live births were registered in the East of Scotland during the period 01/01/2004 to 31/12/2013, with 105 of these children having a clinical diagnosis of RS. Thus, incidence over the 10-year study period was 1 case per 2685 live births. Cases ranged from 5 to 19 per year, with a median of 9 annual cases. No trends in annual incidence were observed over the 10-year study period (**Figure 1**). 56% of infants were male. Median gestational age was 39 weeks, with 13% of infants born prematurely at 28–36 weeks gestation. Median birth weight was 3180g (range 1135-4500g).

Clinical data were available for 100/105 cases. 75% of infants had isolated RS, and 25% had RS+ (a combination of RS and an associated syndrome or RS with a unique set of additional malformations that did not constitute a recognised syndrome). The most prevalent syndromes were Stickler Syndrome (n=8) and Treacher Collins Syndrome (n=3) (**Table 1**).

A family history of cleft palate or other orofacial abnormality was present in 12 cases, and was more common in infants with RS+ (n=7) than isolated (n=5) RS (p=0.03). Prenatal diagnosis was rare; antenatal ultrasound findings consistent with RS were identified in 9 cases (micrognathia, n=7; cleft palate, n=2). Four children had risk factors for intrauterine compression (oligohydramnios, n=2; uterine fibroids, n=1; twin pregnancy, n=1). Excessive alcohol intake during pregnancy was reported in 5 cases, and drug misuse in 8 cases (Methadone, n=8; Diazepam, n=6; misuse of ≥ 3 substances, n=4). An additional four children were exposed to potentially teratogenic prescription medications in utero (Amitriptyline, n=2; Sodium valproate, n=1; Misoprostol, n=1).

Signs of upper airway obstruction (UAO) were noted to have been present in 93% of infants. Airway interventions were required in 63% of infants, whilst 37% were managed with prone or side-lying positioning alone. The most commonly used airway intervention was a nasopharyngeal airway (NPA), which was utilised in 53% of all cases. The median duration of NPA insertion was 18 weeks (range 1 – 36 weeks). Eleven children who were successfully managed with a long-term NPA had been initially managed with a different type of airway adjunct, including endotracheal intubation (ETT) in eight cases and continuous positive airways pressure (CPAP) in two cases. CPAP was used exclusively as a hospital-based intervention, and was not continued beyond hospital discharge in any case. Four children (3 RS+) had an unsuccessful trial of NPA and proceeded to definitive surgical airway management, with 7 children in total requiring surgical airway management (tracheostomy, n=4; tongue-lip adhesion (TLA), n=3), one of whom underwent tongue suture removal prior to hospital discharge and was subsequently managed with NPA.

64% infants with RS required feeding support with nasogastric feeds, and 7% (n=7) required surgical feeding via gastrostomy or jejunostomy. All children who received surgical feeding support had RS+ (**Table 2**).

DISCUSSION:

Our study found an incidence of RS of 1 case per 2685 live births, which remained stable across the 10-year study period. Our reported incidence is significantly higher than described by previous epidemiological studies.

This is the first population-based study of the incidence of RS in the United Kingdom since Bush and colleagues reported a RS incidence of 1 in 8500 live births.³ Bush included infants with cleft palate who were hospitalised for at least 28 days with respiratory or feeding difficulties, such that mild cases of RS may have been missed, a conclusion further supported by the high mortality rate (21%) which suggests a more severe RS phenotype than observed within our cohort.³

Two landmark studies have since described RS incidence in other European countries. First, an incidence of 1 case of RS per 14000 live births was reported by Printzlau and colleagues from a 10-year Danish population-based study, using a national cleft palate registry for case identification.² In this study, RS was defined as the coexistence of micro- or retrognathia, cleft palate, and respiratory distress. Secondly, a birth prevalence of RS of 1:8,850 was reported from a prospective national surveillance study in Germany which utilised a reporting card methodology,¹ and a case definition of micro- or retrognathia in association with either cleft palate or signs of clinical compromise (UAO, feeding difficulties, or weight <3rd centile). The authors acknowledged that mild cases not requiring paediatric inpatient management may have been missed thus underestimating prevalence.

Two further recent studies have pointed towards a higher RS incidence. Paes and Breugem reported an incidence of 1 in 5600 live births in the Netherlands, using the same case definition as Printzlau.⁴ They identified cases from two distinct data sources; the Dutch Cleft

Registry, and case-note review of children with cleft palate admitted to three tertiary paediatric centres. Incidence was estimated as only 1 in 8600 before including cases identified from hospital records, indicating a risk of incidence underestimation when a cleft registry is the sole data source.

A yet higher incidence of 1 case per 3 130 live births has been described in the USA, from a study which utilised a hospital admissions database (Kids' Inpatient Database; KID)⁹ for case ascertainment.⁵ RS was assumed in all cases where ICD-9 codes for micrognathia and cleft palate coexisted. The higher incidence described may be partly attributable to the broad case definition used, and partly to the omission of non-hospital births from denominator data. However, it should be noted that 77% of infants (406/529) underwent surgical airway management, suggesting that clinically significant UAO was present in the majority of cases and reducing the likelihood of substantial over-diagnosis.

Epidemiological studies of RS are limited by the widespread variability in diagnostic criteria used.¹⁰ Such diagnostic inconsistency is illustrated by the various differing case definitions used in the above studies, and has been identified as a barrier to ascertainment of true incidence. Our chosen case definition of micrognathia, glossoptosis, and cleft palate, which is the definition most commonly used by medical professionals involved in RS management,^{6,7} is arguably more inclusive than criteria used in some previous studies. Inclusion of cleft palate was necessary for case identification, as an established registry for this patient group exists in our region and cases of missed cleft palate are rare. We chose to include infants without signs of respiratory distress at presentation as this can be a late or subclinical finding.¹¹⁻¹³ An Australian case series noted that UAO presented beyond 24 days of age in 7/10 infants with RS, and that 6/7 infants had faltering growth which normalised with

alleviation of UAO. Thus, subclinical respiratory compromise may precede the onset of clinical symptoms.¹³ The recent German surveillance study also noted faltering growth in association with undertreated UAO, with treatment of UAO resulting in improvement in weight SD scores.¹

There are several possible explanations for the higher incidence of RS identified by our study. RS incidence may have been underestimated in previous epidemiological studies due to undercounting, by omission of mild cases without overt UAO or need for hospital admission.¹⁻³ Recognition bias could potentially be a factor given that our cases were diagnosed by a single regional cleft service. However, over-diagnosis of RS in our cohort appears unlikely given the high prevalence of UAO symptoms (93%), which is similar to the UAO prevalence (89%) reported by Maas and Poets.¹ Confidence can also be taken from the fact that the majority of infants in our cohort received tertiary paediatric care, where assessment of UAO and decisions about airway management were overseen by a team of respiratory paediatricians. UAO assessments were made clinically, and in cases where clinical assessment was unclear or equivocal a sleep study (limited channel cardio-respiratory polygraphy) was carried out. The requirement for active airway management in 63% of cases is comparable to reports from numerous studies of RS management across many different settings and populations,¹⁴⁻¹⁷ again suggesting that infants in our cohort had 'true' and clinically significant RS.

The high incidence of RS could alternatively relate to a different risk factor profile in our population. The aetiology of RS is believed to be multifactorial, including a genetic predisposition and intrauterine exposure to compressive forces or environmental toxins. A family history of orofacial clefts was present in 12% of cases, increasing to 30% amongst

infants with RS+, which is comparable to the 13-27% reported by previous studies and supports a genetic contribution to aetiology.¹⁸ Risk factors for intrauterine restriction of mandibular growth were present in 4%, and excessive maternal alcohol consumption in 5% cases. The most common antenatal drug exposure in our cohort was to Methadone, a maintenance therapy for opioid dependence. Published data from 2012/13 Scottish maternity records reports misuse of opioids (including prescribed Methadone) or multiple drug types in 1.6% of Scottish mothers.¹⁹ Our finding that methadone was used by 8% mothers of infants with RS may therefore be seen as disproportionately high. Methadone has historically been considered as non-teratogenic. However, Cleary and colleagues recently identified an increased incidence of RS amongst infants with intrauterine Methadone exposure (1 in 155) compared with non-exposed (1 in 7552) infants (relative risk 48.8, 95% CI 14.7 - 161.9). This was substantially higher than the increased risk of non-RS orofacial clefts in Methadone exposed infants in the same population (relative risk 5.4, 95% CI 1.7 - 17.3; statistics derived from published data).²⁰ Of interest, a recently published national prevalence study of opioid use in pregnancy in Denmark (where RS incidence of 1:14,000 live births has been reported) identified opioid use in 0.06% of pregnancies which is substantially lower than amongst Scottish mothers.²¹ The same study identified congenital malformations in 10.4% of methadone-exposed pregnancies which was higher than rates seen amongst non-exposed infants or those exposed to other opioid types. However, these apparent associations may not be due to Methadone-related teratogenicity and could equally be explained by confounding factors, for example differences between exposed and non-exposed mothers in terms of nutritional status, socioeconomic background, or rates of exposure to other potentially harmful substances (e.g. alcohol or other illicit drugs). Further research including well-designed prospective studies is needed investigate this association more definitively.

In our cohort, over half of infants were managed successfully with NPA, which is our first-line intervention for infants with evidence of moderate to severe UAO, as assessed either clinically or using cardio-respiratory polygraphy. We reserve surgical management for cases of moderate to severe UAO that fail to improve following satisfactory placement of an appropriately sized NPA, as assessed radiographically and where necessary using flexible nasendoscopy. We regard CPAP use and ETT insertion as short-term measures which are reserved for the acutely obstructing infant who cannot be quickly stabilised with NPA, or as a bridge to surgery. Using this approach, treatment failure with NPA was rare in our population, and was significantly associated with a diagnosis of RS+. Prematurity or lower birth weight did not preclude successful NPA use. Our longstanding institutional experience of NPA use in RS is that this intervention is effective, well-tolerated, and can be easily taught to caregivers. Successful introduction of NPA and caregiver training does not require a protracted hospital admission, as demonstrated by the median 10-day admission following NPA insertion in our cohort. However, this streamlined approach relies on the collective experience of the multidisciplinary team, in particular inpatient nursing staff and respiratory nurse specialists. Home management with NPA has similarly been described as safe and effective by several other authors.^{11,12,16,22} Abel and colleagues reported similar findings to ours with successful use of NPA in 61% of infants with RS, with treatment failure in only 18% of cases.¹¹

There is heterogeneity of approach to management of UAO in RS, with no evidence-based clinical practice guidelines to direct management.²³ This lack of uniformity in approach was highlighted by a recent survey of practices across 101 European centres, which showed that NPA, CPAP and palatal plates were strongly favoured in the UK, France and Germany, respectively.⁷ Only 7% of our cohort required surgical airway management which concurs

with the findings of recent large studies.¹ However, significantly higher rates of surgical intervention (including distraction osteogenesis and tongue-lip adhesion) and tracheostomy of 19-77% have been reported in several studies which are largely from North American centres.^{5,24-27} This wide variation in practice with an apparent geographical pattern suggests that physician or treatment centre preferences, rather than clinical necessity, may direct RS management.

In conclusion, we report RS incidence in the East of Scotland as 1:2685 live births, which is substantially higher than rates reported by previous UK epidemiological studies. Recognition bias is unlikely given the high prevalence of upper airway obstruction requiring active airway management. Possible explanations include an underestimation of RS incidence by previous studies due to omission of cases with subclinical UAO, or the presence of a different risk factor profile in our population. A possible association between intrauterine Methadone exposure and RS development warrants further investigation. We are currently verifying and further investigating these findings through a UK-based national prospective surveillance study of RS incidence and management, in collaboration with the British Paediatric Surveillance Unit (BPSU), which commenced in January 2016.

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