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Initial treatment and early weight gain of children with Robin Sequence in Germany: a prospective epidemiological study

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ABSTRACT

Background To investigate birth prevalence of Robin Sequence (RS), distribution of implemented treatments and factors influencing weight gain during initial hospitalisation.

Methods Prospective population-based survey (August 2011–July 2013) on new hospital admissions of infants with RS in Germany. RS was defined as retrognathia/micrognathia and at least one of the following: upper airway obstruction, snoring or hypoxaemia; glossoptosis; feeding difficulties; failure to thrive; cleft palate or RS-associated syndrome. Birth prevalence was calculated using data from the National Bureau of Statistics and in-hospital weight gain evaluated by calculating differences in SD scores (SDS) for weight. Comparisons between cohorts were performed using the Wilcoxon/Kruskal–Wallis test or Fisher's exact test.

Results 151 patients with RS could be verified resulting in a birth prevalence of 11.3 per 100 000 live births. Orthodontic therapy (feeding plate or pre-epiglottic baton plate, PEBP) was applied most frequently (107 infants), followed by prone positioning (97 infants). Tracheotomy was rarely performed (n=7). For 115 infants, implementation of more than one intervention was reported. Infants with serious respiratory difficulties during initial hospitalisation (n=58) showed a more pronounced decrease in SDS for weight (median (IQR) −0.81 (−1.32 to −0.26) vs −0.48 (−0.86 to 0.02); p=0.008) whereas treatment with PEBP was associated with better weight gain (SDS-difference for weight −0.37 (−1.06 to 0.02) vs −0.74 (−1.09 to −0.35); p=0.022).

Conclusions Non-surgical management is preferred for infants with RS in Germany. The extent of upper airway obstruction seemed to influence in-hospital weight gain, while use of the PEBP was associated with improved early weight gain.

What is already known on this topic

- Pierre Robin Sequence (RS) is a rare condition for which epidemiological data are scant.
- Treatment approaches range from prone positioning to tracheostomy.
- Little is known about the effects of treatment on weight gain and upper airway patency.

What this study adds

- Birth prevalence of RS in Germany is 11.3 per 100 000 live births.
- Initial treatment in Germany predominantly involves orthodontic therapy.
- Weight gain seems to be affected by the severity of upper airway obstruction, while use of the pre-epiglottic baton plate might be associated with improved weight gain.

INTRODUCTION

Characteristic features of infants with Robin Sequence (RS) are a hypoplastic mandible and glossoptosis resulting in upper airway obstruction (UAO) with or without a cleft palate.[1] It is a very heterogeneous disorder and the causative pathogenetic event is unknown.[2] Data on the incidence are scant. The main functional problems associated with RS are UAO and failure to thrive.[2–4] Growth issues in infants with RS are related to different causes. On one hand, RS-associated feeding difficulties may result in reduced weight gain, on the other hand, underlying genetic and metabolic disorders might impair growth.[2 5 6] Not least, high-energy expenditure due to breathing difficulties resulting from UAO is considered to be an important source of faltering growth in these infants.[2 5 6]

Interventions used to resolve breathing and feeding difficulties in RS infants are heterogeneous. We present data from a 2-year prospective population-based study in Germany that aimed to investigate the birth prevalence of RS, distribution of implemented treatments and factors influencing weight gain during the initial hospitalisation.

METHODS AND PATIENTS

This prospective epidemiological study was conducted as part of the Surveillance Unit for Rare Paediatric Conditions in Germany (ESPED). All paediatric departments (459 contact persons) received monthly reporting cards asking them about new admissions of infants with RS between August 2011 and July 2013. Reports on the mailing card prompted immediate mailing of an anonymised three-page questionnaire. An anonymised medical report was also requested. Further details and additional online material including an English translation of the questionnaire have been reported elsewhere.[7] Infants reported to have required bagging, ventilation via a nasopharyngeal tube, endotracheal intubation or tracheotomy to resolve acute respiratory crisis during their initial hospitalisation, were defined as a subgroup of infants with apparent serious UAO.

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Captured were all infants receiving inpatient healthcare in a paediatric unit during their first year of life independent of the indication leading to hospitalisation. Infants with mild expressions of RS never admitted to a paediatric unit during this period were not included. Inclusion criteria were retrognathia/micrognathia in patients between 0 and 12 months of age, as suspected by the attending physician, showing at least one of the following additional criteria: UAO, including subcostal/intercostal retractions, snoring or hypoxaemia, glossoptosis, feeding difficulties, weight <3rd percentile at admission, cleft palate or RS-associated syndrome. We used this rather broad definition to minimise potential under-reporting and are aware of the fact that no consensus on diagnostic criteria for this disorder yet exists. An underlying genetic disorder was diagnosed either by the attending paediatrician or a geneticist, information on how many syndromic diagnoses were ascertained by genetic testing is lacking. Patients who were reported in duplicate or did not meet inclusion criteria were excluded. To determine the birth prevalence of RS, we used data from the National Bureau of Statistics on the number of births in Germany.[8]

As this is an explorative study without a primary hypothesis, no sample size calculations were done. Descriptive statistics were applied to characterise the study population. To evaluate weight gain, SD score (SDS) for weight was computed using the Microsoft Excel add-in LMS Growth (V.2.14; http://www.healthforallchildren.com/?product=lmsgrowth). The reference population for this programme is the British 1990 growth reference fitted by maximum penalised likelihood.[9 10]

Data are presented as median (IQR). Comparisons between cohorts were performed using the Wilcoxon/Kruskal–Wallis test or Fisher's exact test. To account for the impact of intrauterine growth restriction and gender, SDS differences ($SDS_{discharge}$–$SDS_{admission}$) for weight were calculated to illustrate in-hospital weight gain. Statistical significance was assumed at $p<0.05$. Analyses were performed with JMP V.11.1 (SAS Institute, USA).

The study protocol, including a parental consent waiver, was approved by the ethics committee of Tuebingen University Hospital.

RESULTS

A total of 182 patients with RS (age 0–12 months at admission) were reported to the study centre between August 2011 and July 2013. Detailed information via returned questionnaires was available for 174 infants, yielding a response rate of 96%. Of these 174 cases, 151 could be verified, nine were erroneous notifications, not meeting inclusion criteria, and 14 were duplicate cases. There were 144/151 patients who met two or more additional criteria. Weight <3rd percentile at admission was never reported as an additional criterion alone.

Given 662 685 live births in Germany in 2011 and 673 544 in 2012, a birth prevalence of 11.3 per 100 000 live births is the result. For details of patient characteristics, see table 1.

Median length of initial hospitalisation was 19 (11–38) days. Considering SDS for weight, there was a decrease by 0.59 (1.08–0.11) during admission.

For 138/151 patients, information on implemented therapy was provided. In 88/138, prone positioning was applied in combination with additional treatment modalities, whereas it was reported as the sole intervention in only 9/138 infants. In 11 infants, a surgical intervention for RS was reported during the initial hospitalisation. For 115/138 infants, implementation of more than one intervention was reported (for details, see table 2); unfortunately, our data did not allow further differentiation whether interventions in one child were applied contemporaneously or consecutively. For example, 18 infants treated with pre-epiglottic baton plate (PEBP) were also supported by continuous positive airway pressure (CPAP) during their initial hospitalisation, but it is unclear whether CPAP was required in addition to PEBP treatment or was limited to periods before PEBP treatment was initiated.

Fifty-eight children (44% of n=131 with information supplied) experienced respiratory difficulties necessitating emergency intervention for respiratory support (for definition see the Methods and Patients section) during their hospital stay. This subgroup showed a significantly more pronounced decrease in SDS for weight during their hospitalisation compared with infants without a need for emergency intervention (figure 1, p=0.0078).

At discharge, 76 children (55% of n=139 with information supplied) still received nasogastric tube feeding. The frequency of nasogastric tube feeding at discharge was significantly higher in infants with syndromal RS (71% of n=34 with available information) compared with those with isolated RS (p=0.04),

Table 1 Patient characteristics

Total number	151
Initial presentation	
Retrognathia	151 (100%; n=151)
Breathing difficulties	120 (87%; n=138)
Glossoptosis	100 (81%; n=124)
Feeding/swallowing difficulties	126 (89%; n=142)
Weight <3rd percentile at admission	33 (29%; n=115)
Cleft palate	114 (83%; n=137)
RS-associated syndrome	40 (43%; n=93)
Female	72 (48%; n=150)
Gestational age at birth (weeks) Median (IQR)	39 (37.8–40)
Birth weight (g) Median (IQR)	2990 (2525–3494)
Age at admission (days) Median (range)	0 (0–296)
Weight at admission (g) Median (IQR)	3000 (2625–3380)
Weight at discharge (g) Median (IQR)	3420 (2948–3988)

n, number of questionnaires with data provided; RS, Robin Sequence.

Table 2 Implemented therapies

Infants with available information on implemented therapies	138*/151
Prone positioning	97
Continuous positive airway pressure	48
Nasopharyngeal airway	29
Orthodontic therapy	
Feeding plate	56
Pre-epiglottic baton plate	51
Tracheotomy	7
Oral and maxillofacial surgical therapy	
Osteoplastic distraction	0
Mandibular traction	3
Glossopexy	1
Functional therapy (orofacial regulation therapy, eg, Castillo Morales)	82

*For 115/138 infants, more than 1 intervention was reported.

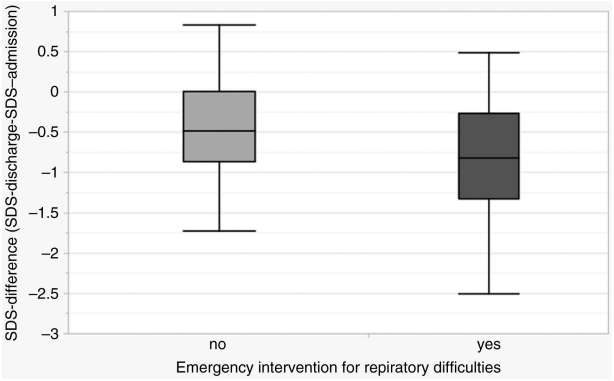

Figure 1 Comparison of SD score (SDS) difference for weight between infants with and without emergency intervention for respiratory difficulties. Box-and-whisker plots are shown, with boxes representing medians and quartiles and whiskers according to the definition of Tukey (extension from the end of the box to the outermost data point that falls within the distance 3rd quartile+1.5*(IQR) and 1st quartile−1.5*(IQR)); p=0.0078.

whereas, there was no significant difference in the change in SDS for weight during hospitalisation between these subgroups (p=0.19). Twenty-eight infants (20% of n=138 with information supplied) were reported to receive a hypercaloric diet at discharge.

Infants provided with a PEBP demonstrated better weight gain during their initial hospitalisation (SDS-difference for weight −0.37 (−1.06 to 0.02) vs −0.74 (−1.09 to −0.35); p=0.022).

Twenty-nine infants with RS (19%) were treated at the authors' institution, a referral centre for infants with RS and other craniofacial malformations. Comparing this cohort to all other infants in this study, there was a significantly better weight gain during the initial hospitalisation in infants treated at the authors' institution (table 3). This is also true if analysis is restricted to infants with isolated RS (83% of N=24 with information supplied; p=0.0033). Additionally, more infants were discharged without nasogastric tube, whereas length of hospital stay was similar (table 3).

DISCUSSION

The 151 infants reported here correspond to a birth prevalence for RS of 11.3 per 100 000 live births. This result is in line with our recently published first-year data of this survey revealing a birth prevalence of 12.4 per 100 000 for Germany[7] and represents a more reliable estimate with an additional year of data collection. Nevertheless, these data might still represent an underestimation of birth prevalence, as some mild cases of infants with RS may have been missed if they had never been hospitalised in paediatric units. Furthermore, no consensus on diagnostic criteria for this disorder exists, which again is complicating incidence estimations. Regarding implemented treatment, it is striking that in the vast majority of infants more than one therapeutic intervention was covered. Orthodontic therapy (feeding plate or PEBP) was most commonly reported (107 of n=138 with information supplied) followed by prone positioning (97 of n=138). The latter as a sole intervention, however, was only rarely perceived as a sufficient treatment modality (9/138). This is in contrast with other case series describing prone positioning as a sufficient treatment in 50%–80% of infants with RS.[11–13] Surgical interventions, dominating the international literature, apparently also played only a minor role in our national enquiry (see table 2). Use of the PEBP was frequently reported, with an increasing frequency during the second year of our study (19/76 during the first year[7] vs 32/62 in the second). The PEBP has been proven as an effective treatment approach to improve UAO in infants with RS in a randomised clinical trial.[14]

A substantial proportion of infants experienced at least one event with serious respiratory difficulties during their initial hospitalisation necessitating emergency respiratory support. This emphasises the need for adequate monitoring of affected infants and treatment relieving UAO.

Weight gain during the initial hospitalisation was generally poor with a substantial decline in SDS for weight. Interpretation of these data is complicated by a relative short length of initial hospitalisation (median 19 days) and the fact that many infants were admitted on their first day of life so that a certain degree of weight loss could be expected during their first days of admission. On the other hand, the finding of poor weight gain is in line with other reports demonstrating impaired weight gain in infants with RS.[6 15 16] Underlying reasons remain unclear, but airway obstruction is supposed to be a major cause.[2 16] This hypothesis is supported by our finding that infants with respiratory difficulties necessitating emergency intervention during their postnatal hospitalisation showed significantly poorer weight gain than those without (figure 1). In this population-based observational study, treatment with the PEBP was associated with a significantly better weight gain during initial hospital stay (p=0.022), though potential interference by other interventions such as CPAP cannot be excluded. These data also support the hypothesis that airway obstruction, which is improved by the PEBP,[14] might be a contributor to impaired growth. Further evidence in this respect results from a recent systematic review on mandibular distraction osteogenesis in infants with RS that showed improved growth rates after

Table 3 Infants treated at the author's institution

	Authors' institution	Other infants	p Value (Wilcoxon or Fisher's exact test)
Number of infants	29	122	
Length of hospitalisation (days) Median (IQR)	15.5 (12–20)	20.5 (11–44)	p=0.21
Pre-epiglottic baton plate (n/N)	23/29	28/122	p<0.0001
SDS-difference for weight ($SDS_{discharge}-SDS_{admission}$) Median (IQR)	−0.03 (−0.5 to 0.12)	−0.74 (−1.16 to −0.33)	p<0.0001
Emergency intervention for respiratory support (n/N)	6/28	58/114	p=0.0057
Nasogastric tube at discharge (n/N)	7/28	69/111	p=0.0004

N, number of questionnaires with data provided; SDS, SD score.

initiation of that treatment.[17] In the future, prospective studies comparing various treatment approaches have to show the impact of different treatment modalities on weight gain in infants with RS.

Despite failure to thrive in a majority of infants with RS, only a minority (20%) received hypercaloric diet at discharge. It, thus, seems likely that there is insufficient attention to growth issues in infants with RS, at least in Germany.

The majority of infants treated at the authors' institution were provided with the PEBP (table 3) and obtained additionally intensive feeding training and functional orofacial regulation therapy (Castillo Morales). This cohort demonstrated significantly better and adequate weight gain (table 3) and was more frequently discharged without a feeding tube. In addition to potentially positive effects of PEBP and/or functional orofacial regulation therapy, other factors not sufficiently explored in this survey, for example, nutritional staff support and staff resources in general, may have influenced growth outcomes. Furthermore, we did not investigate the effect of these two treatment options separately. Here again, future interventional studies have to show whether a combination of orthodontic therapy with PEBP and orofacial regulation or one of both as a sole intervention might be a clue to preventing faltering growth and reducing feeding difficulties in infants with RS.

Nationwide data acquisition and growth data derived from a population-based investigation are strengths of this study. On the other hand, recall bias poses a limitation, as we obtained information on cases only some weeks or even months after admission, thus leading to potential blurring of documented information or even loss of information, both potentially biasing study results. Additionally, we have no data on the detailed sequence of treatment modalities or their duration, and our attempts to evaluate further data on weight development during the first year of life failed due to a proportion of missing data.

CONCLUSION

Non-surgical management is preferred in infants with RS in Germany, with orthodontic therapies being most frequently applied. Our population-based data support the hypothesis that UAO may play an important role in growth issues of infants with RS. Use of the PEBP seems to be increasing in Germany and further prospective studies have to show whether the hypothesis can be ascertained that this treatment approach is associated with improved weight gain and a reduction in feeding difficulties, the latter at least if combined with additional functional therapy.

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Contributors CM provided substantial contributions to the acquisition, analysis or interpretation of data for the work, wrote the first manuscript draft, gave final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CFP provided substantial contributions to the conception and design of the work, reviewed the work critically, gave final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None.

Ethics approval Ethics Committee of Tuebingen University Hospital.

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Notes